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The Synthesis of Acetylisophthalic Acid for the Double Capping of beta-Cyclodextrin

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The Synthesis of
Acetylisophthalic Acid
for the Double Capping of β-Cyclodextrin

A Thesis

Presented to

The Faculty of the Department of Chemistry

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In Partial Fulfillment

Of the Requirements for the Degree of

Master of Arts

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by

Shuchi Sharma

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APPROVAL SHEET

This thesis is submitted in partial fullfillment of the requirements for the degree of

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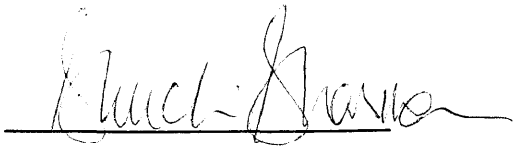
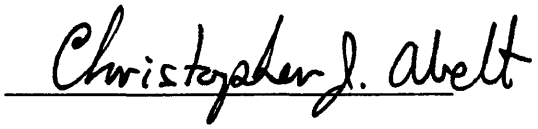


Shuchi Sharma

Approved, August 1993



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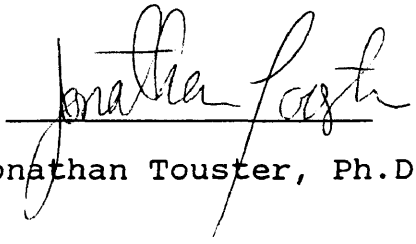

Jonathan Touster, Ph.D.

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ABSTRACT

Synthetic routes into 5-acetylisophthalic acid are explored. The most promising route was frustrated by the poor cyanation of 3′,5′-dibromoacetophenone.

Attempts were made to circumvent this step. The best alternative route involved the cyanation of 3′,5′-dibromophenylethanol, but yields were still poor. The acetylisophthalic acid was to be used as a double capping agent for β-cylcodextrin.

THE SYNTHESIS OF ACETYLISOPHTHALIC ACID FOR THE DOUBLE CAPPING OF β-CYCLODEXTRIN

INTRODUCTION

Cyclodextrins have come to the forefront of chemistry research because of their widespread industrial and research applications. Discovered in 1891 by Villiers,[1] and first described in literature by Schardinger,[1]cyclodextrins are formed by the cleaving action of an enzyme, the amylase of Bascillus macerans on starch. The starch digests consist of α-,β-, and γ -cyclodextrins, units of 6,7,and 8 linkages of D(+)-glucopyranose units.[1] Doughnut shaped in nature, cyclodextrins are of great interest because they can complex other molecules in their hydrophobic cavity and form inclusion compounds.[1] The extent to which these inclusion complexes form depends on certain characteristics of the cyclodextrin employed, (diameter, shape, and hydrophobicity). [1] Weak hydrophobic interactions and hydrogen bonding with the substrate sustain complex formation. [1]

Cyclodextrins can be derivatized with molecules that serve as caps, enhancing their utility as an inclusion cavity.[2] Capping of the host molecule causes the substrate to bind more firmly within the cavity. Advantages of the host-guest relationship with cyclodextrin include enhanced guest stability provided to the guest compound. [1]

Within the industrial sector, cyclodextrins have found a niche in several different areas due to the diversity of their applications. Already many uses have been patented in

the pharmaceutical, cosmetic and food industries.

The pharmaceutical industry currently uses cyclodextrins for a variety of purposes such as the increased release of heavily soluble drugs.[3] In the last decade, the published papers and patents held in conjunction with the application of β- cyclodextrins in pharmaceuticals have determined the two most important fields of their application.[3] These applications include an enhancement of the bioavailability by improving the solubility of the water-insoluble or slightly soluble drugs and a stabilization against oxygen, decomposition, and hydrolysis.[3]

The agricultural and food industries have utilized cyclodextrin as well. Stabilization of volatile herbicides and insecticides via molecular encapsulation has evolved into a routine measure.[3] A recently developed method for the production of powdered alcoholic beverages has also emerged due to the facility of their inclusion in β-cyclodextrin.[3]

Along with its industrial applications, the far reaching potential of cyclodextrin in catalysis studies is also being investigated by many research scientists. Natural enzymes incorporate substrates into their hydrophobic cavities, thereby governing their activity. By forming inclusion compounds and complexing with substrates, cyclodextrin's mimic a number of enzyme substrate systems.[3] Cyclodextrins are able to catalyze reactions, once the complexation with the substrate has occurred, serving as a

miniature enzyme model system. [3] Cyclodextrin allows acceleration of certain chemical transfer reactions, shows hydrophobic interactions, forms stereospecific complexes and provides an inner surface with dielectric properties different from the outside solution, all characteristics of many enzyme systems.[3] Cyclodextrins also catalyze a number of other reaction types including the cleavage of esters, amides, and organophosphates, decarboxylation and intramolecular acyl migration.[1]

Derivatized cyclodextrins show much promise for uses in enzyme catalysis studies. The diversity of possible derivitizing agents also allows for applications in many other areas of cyclodextrin research, including its use in photochemical studies. For instance, pinacolization of doubly substituted cyclodextrin would provide a very rigid and well defined cap, potentially more useful than caps currently used. We attempted the synthesis of acetylisophthalic acid, to eventually be used as a double capping agent of cyclodextrin. Pinacolization should provide the first cap which is attached to β-cyclodextrin at four positions.

CYCLODEXTRIN:

Cyclodextrins, also known as cycloamyloses or cycloglucans are cyclic polysaccharides, consisting 6, 7, or 8 D(+)glucopyranose units linked in an α-(1,4) fashion. They are designated by greek letters: α- denotes six units of linked saccharides, β- denotes seven and γ- denotes eight. As mentioned earlier, cyclodextrins were first isolated and characterized by Schardinger in the 1950's, who treated starch with the amylase of Bascillus Macerans. The cleaving action of the enzyme on starch resulted in a mixture of α-, β-, and γ- along with a few higher cyclodextrins comprised of 16-21 glucose units. Cyclodextrins with fewer than six residues do not occur because of ring strain.

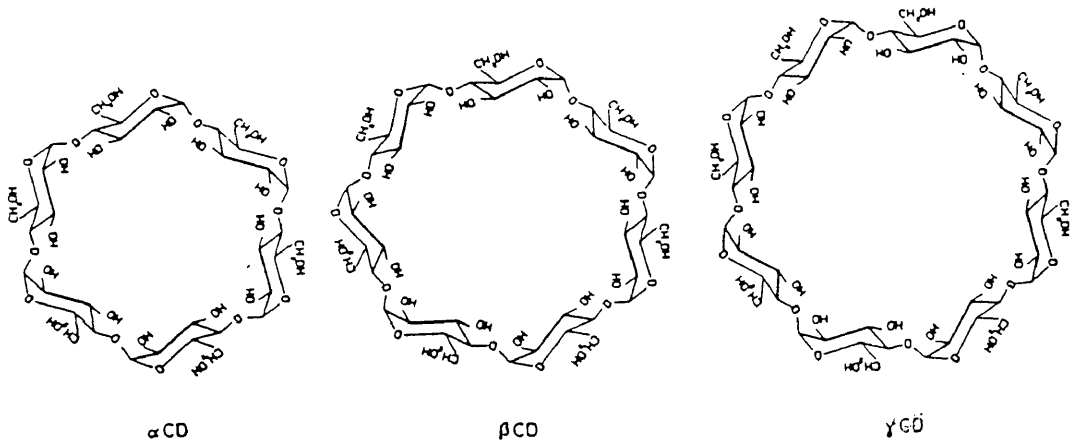


Figure 1. Structures of α-, β-, γ-Cyclodextrin.

In cyclodextrins, the glucopyranose units sit in a

relatively undistorted C1 chair conformation. The secondary hydroxyl groups (on the C-2 and C-3 carbons of the glucose units) are found on one face of the cyclodextrin, while the primary hydroxyl groups are found on the other side. The interior of the molecule is hydrophobic, comprised of C-H bonds and nonbonding electron pairs of the glycosidic electron bridges that donate electron density to the inside of the cavity. Cyclodextrin molecule itself is relatively hydrophilic.

The cavity within cyclodextrin is "V" shaped. The rotating primary hydroxyl groups can block the cavity , but the secondary hydroxyl groups, because of their more rigid conformation, cannot. Therefore, the overall appearance of the a molecule is analagous to a torus with the primary face possessing a slightly more narrow circumference than the secondary face. The limited rotation

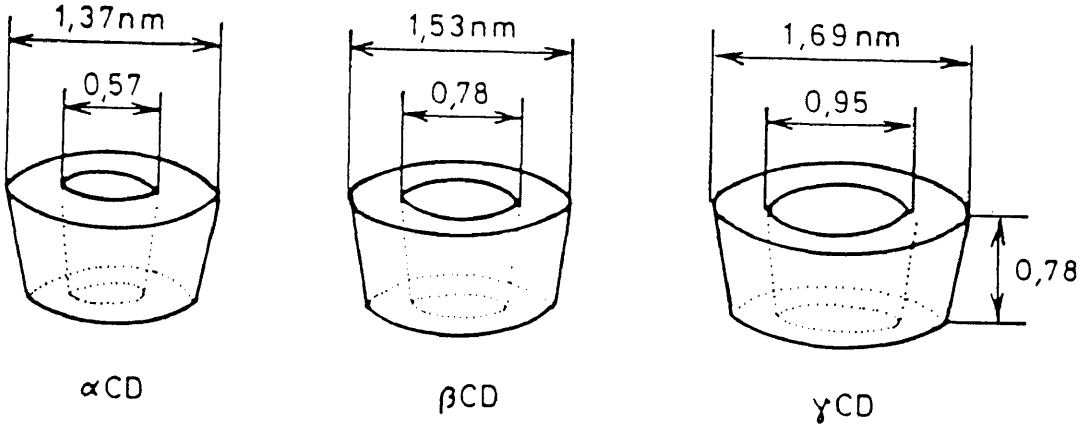


Figure 2. Dimensions of α-, β-, γ-Cyclodextrin

of the glucopyranose units allows the cyclic structure of the

molecule to be strengthened by hydrogen bonding.

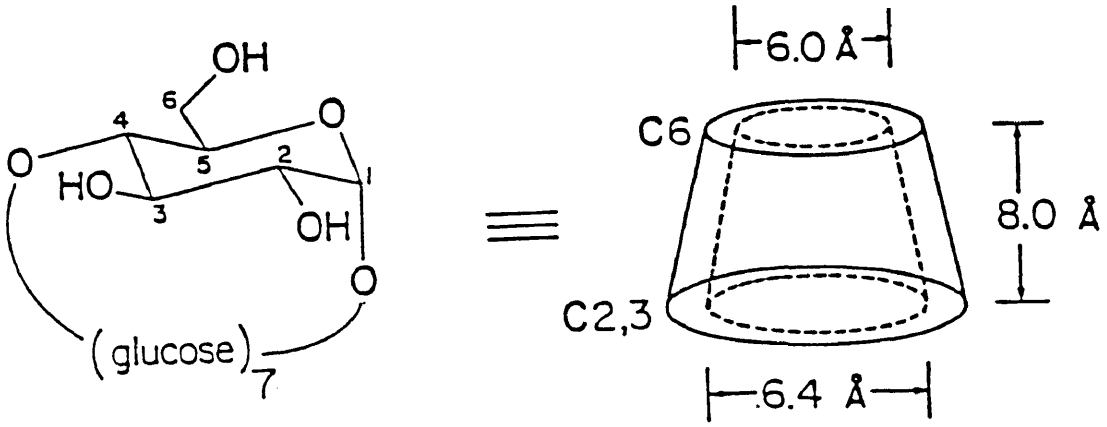


Figure 3. The Molecular Structure of δ-cyclodextrin.

The cyclization of the chain of glucose residues is favored over the corresponding linear form. α-, β-, and γ-cyclodextrins have a lower free energy than linear glucose chains. Although the enthalpy component of the free energy is higher for α-, β-, and γ- cyclodextrins, the entropy terms compensate. This positive entropy change results from the reassembly of the water molecules around the glucopyranose units once the structure has been formed due to their decreased surface area.[1]

β-cyclodextrin has been more widely used for complexation and derivatization studies than α- or γ- cyclodextrin. Its greater rigidity deriving from complete secondary hydrogen bonding inside its cavity, results in a tighter binding of the substrate. In α-cyclodextrin the ring of hydrogen bonding is incomplete, because, one of the glucopyranose units rotates out of the plane and obstructs the formation of two possible hydrogen bonds. Larger cylcodextrins, are often too flexible

to be used for complexation studies.[4]

INCLUSION COMPLEXES:

The formation of cyclodextrin inclusion complexes is associated with both a favorable enthalpy change and a favorable entropy change. However, classic enzyme-substrate complex formation is more strongly characterized by a favorable entropy change since apolar binding serves as the most prominent cohesive force. Various theories have been propsed to account for the large, favorable enthalpy change that results from cyclodextrin complex formation. It has been suggested that van der Waals interactions which include permanent dipole-induced dipole interactions and London Dispersion forces, exist between host and guest molecules. Also hydrogen bonding between the hydroxyl groups of cyclodextrin and the guest molecule would enthalpically favor binding. Other factors include the release of high energy water molecules from the cyclodextrin cavity as well as the release of strain energy in the macromolecular cyclodextrin ring.[1]

These last two theories explain why inclusion complexes develop most readily in an aqueous solution. Although cyclodextrin complexes substrates readily in dimethyl sulfoxide, the disassociaton constants are much larger than those in water. In an aqueous solution, water molecules

trapped within the cyclodextrin cavity are high in potential energy because they cannot fully hydrogen bond with adjacent water molecules . These cavity-bound water molecules are displaced when cyclodextrin binds a hydrophobic guest.

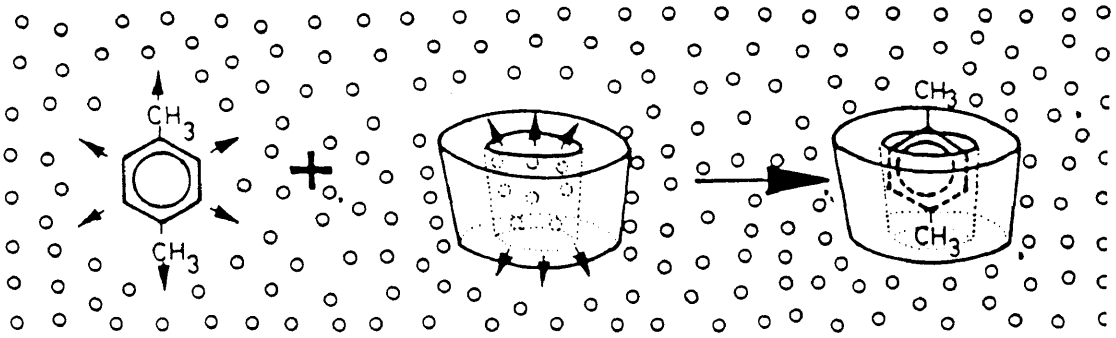


Figure 4. Hydrophobic Inclusion into Cyclodextrin.

Also the ordering of the water around an apolar molecule in solution leads to an unfavorable decrease in entropy. Once this molecule enter the cavity, releasing the water molecules, it not only releases the high energy water moleculed, but it no longer imposes a higher ordering on its neighboring waster molecules. The release of enthalpy-rich water molecules to the rest of the aqueous solution creates a more enthalpy-rich environment.[1]

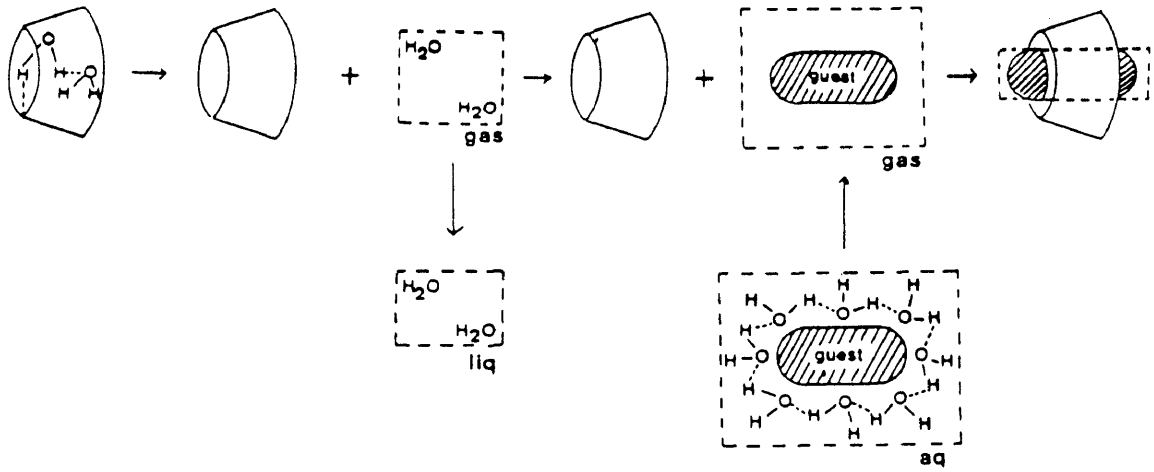


Figure 5. Thermodynamic Factors in Hydrophobic Bonding.

Van der Waals interactions also play a decisive role in the binding of substrates within the cyclodextrin cavity. These forces regulate the geometry of the inclusion complexes, especially in instances in which the substrate is very large. The larger substrates maintain a closer contact with the walls of the cavity and experience more intense van der Waals forces. Calculations using x-ray crystallography have been used to compute energies associated with van der Waals interactions for the host- guest relationship and have shown stong deviations for molecules that were polar (e.g. methanol) and very small (e.g. krypton).

The contribution of hydrogen bonding to substrate binding

has been questioned. Hydrogen bonding occurs between the C6 hydroxyl of cyclodextrin and a polar guest molecule. Although hydrogen bonding is present, no significant evidence has developed to implicate it as a major driving force behind inclusion complex formation.

Although studies have conflicted as to the prevalence of the various factors driving complex formation, Matsui et. al. were able to conclude that all the forces involved favored the generation of the inclusion complex simultaneously.[5]

CAPPING:

One modification of cyclodextrin currently under investigation is capping of the primary face of the molecule. The attachment of specific hydrophobic moieties has been noted to increase the binding strength of various inclusion complexes.

Capping provides a hydrophobic "floor" to the face of the molecule creating a more well defined geometry and thus aiding in anchoring the bound substrate. Without the cap, both ends of the molecule are open, presenting problems associated with the complexation rates of the substrate and the molecule.[6]

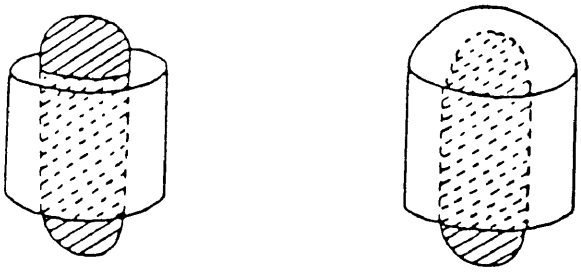


Figure 6. Effect of Capping on Cyclodextrin

According to the Nemethy-Sheraga theory, decreasing the hydrophobic surface exposed to the solvent increases the hydrophobic binding strength. Breslow reports the results of studies which involve substituting the hydroxyl groups of the C6 carbon atoms with hydrophobic groups which gather around the surface of a bound molecule. By substitution on only one hydroxyl group,which constitutes a tether, the hydrophobic moieties are freely rotating, and increase binding strength of a substrate 11-24 times compared to the binding of a substrate in an uncapped cyclodextrin.[6]

Although the binding strength of the modified cyclodextrin substantially increased via this method, a step further step was taken by Tabushi, who reported the capping on the A,C and A,D residues of cyclodextrin.

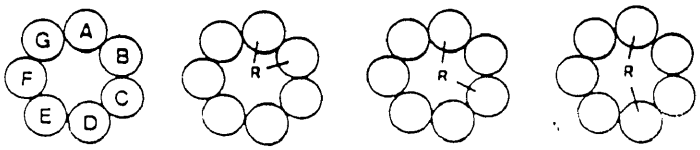


Figure 7. AB-,AC-,and AD-Capping

The bifunctionalized capping of cyclodextrin allows for modeling of production of the more specialized enzymes that require efficient catalytic sites not available via Breslow's "flexible" capping.

A bifunctionalized system can create a more well-defined or rigid geometry, which enhances catalytic rates and substrate binding. Capping is performed using a disulfonyl or dicarbonyl chloride. Mechanistically, the capping occurs via the "looper's walk".

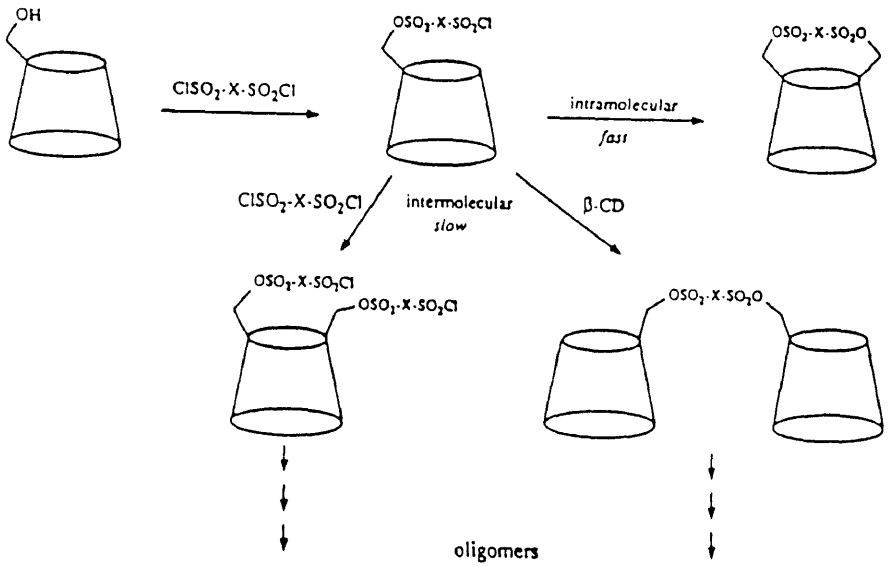


Figure 8. Cyclodextrin Capping: Looper's Walk vs. Oligomerization

Tabushi has shown this reaction occurs via an addition/ elimination reaction, in which one of the primary hydroxyl groups of cyclodextrin attacks the acid chloride. Once the tether attaches to the A glucopyranose unit, the second

functionalization can occur at either the B, C, or D glucopyranose moiety. The types of regioisomers formed depends on a variety of factors, including Most importantly, the direction of approach of an entering group, along with the flexibility of the capping molecule. The most important factor is strain. [7]

Tabushi studied the distribution of regioisomers by reacting β-cyclodextrin with biphenyl-4,4′-disulfonyl chloride, trans-stilbene 4,4′-disulfonyl chloride, and benzophenone-3,3′- disulfonyl chloride. The trans- stilbene 4,4′-disulfonyl chloride and biphenyl 4,4′- disulfonylchloride capping resulted in the A,D isomer, while the benzophenone-3,3′-disulfonyl chloride cap produced the A,C isomer.[7] A regiospecific A,B cap was also developed using *m*-benzenedisulfonyl chloride.[8]

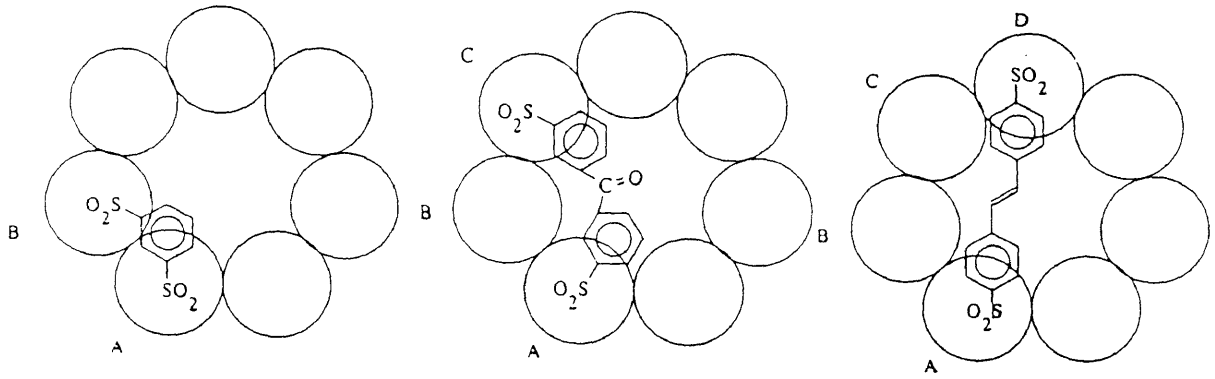


Figure 9. Tabushi's Regiospecific AB-,AC-, and AD-Capping Agents

Along with bifunctionalization of cyclodextrin, Tabushi took the modification of cyclodextrin a step further by successfully preparing a regiospecifically tetrasubstituted cyclodextrin. In his study, benzophenone-3,3′-disulfonyl is used as the double capping agent to produce the A,C- A′,C′ regioisomer. This transannular capping also increases the rigidity of cyclodextrin, creating a cavity with a more significantly well defined geometry.[9]

Double capping of cyclodextrin offers the possibility of further modifications via infra-cap reactions. One such reaction uses photopinacolization of the doubly capped moiety. The molecule is irradiated to induce formation of a pinacol, a more secure and well defined cap.

PHOTOCHEMISTRY:

The ultimate aim of this project is to induce photopinacolization of a doubly capped cyclodextrin molecule.

Photochemical reactions occur as a result of a compound absorbing light. The absorbing molecule must possess an excited state which coincides with the energy of irradiation in order to undergo excitation. Light absorption changes the electronic configuration of the molecule. Although the electron's configuration changes, spin inverion during

excitation is forbidden by quantum mechanical selection rules. These rules state that only after the excitation occurs, spin change can occur by a coupling mechanism leading to the new minimum energy configuration. The excited molecule relaxes by transfering its thermal energy to the solvent. Along with this vibrational relaxation, the excited state can also undergo intersystem crossing. This happens by a mechanism involving the spin inversion of an electron in a half-filled orbital. If the rate of crossing is fast, relative to the rate of the reaction, the inversion leads to a configuration known as the triplet state, characterized by both electrons having the same spin. The triplet state has an energy lower than the first excited singlet state .

Photosensitization can also produce excited states . For triplet sensitization, intersystem crossing is faster than energy transfer to the solvent or reaction from the singlet state. The acceptor molecule reacts with with the triplet state of the sensitizer to form the triplet state of the acceptor molecule. Sensitizers are useful for molecules which undergo slow spin conversion .

Triplet states of carbonyls are long lived enough to undergo chemistry. One of their most common reactions involves the oxygen of the carbonyl abstracting a hydrogen from the solvent or another hydrogen atom donor by the oxygen of the carbonyl group. This abstraction can be either intermolecular or intramolecular. Hydrogen abstraction from the solvent is

often followed by a coupling of the resulting α-hydroxy radicals. Another common occurance is the cleavage of the carbon-carbon bond next to the carbonyl group.

Other reactive excited states include the n-Π^* transition for saturated ketones and the Π-Π^* transition for ketones in a Π-bonding system with extensive conjugation. In the n-Π^* state, an electron from the nonbonding orbital of oxygen moves to the Π-antibonding orbital of the carbonyl moiety. The singlet state is the first to form, but intersystem crossing to the triplet then happens. In the Π-Π^* transition, an electron from the bonding Π orbital is promoted to the antibonding Π^* orbital. [10]

Studies reported on the photochemistry of benzophenone capped β-cyclodextrin by Abelt *et. al.* utilize a photoexcited benzophenone to form a pinacol. Initially, benzophenone is irradiated and excited to its singlet state. This singlet state undergoes intersystem crossing and converts to the triplet state. In its triplet state, benzophenone can abstract a hydrogen from an alcohol, breaking the carbonyl double bond, creating a carbon-centered radical on benzophenone and the alcohol. The radical center of the alcohol than donates a hydrogen atom to an unexcited benzophenone in order to form a more resonance stabilized radical center on the benzophenone. Two radical centers (on the benzophenone) can now couple to form a pinacol.

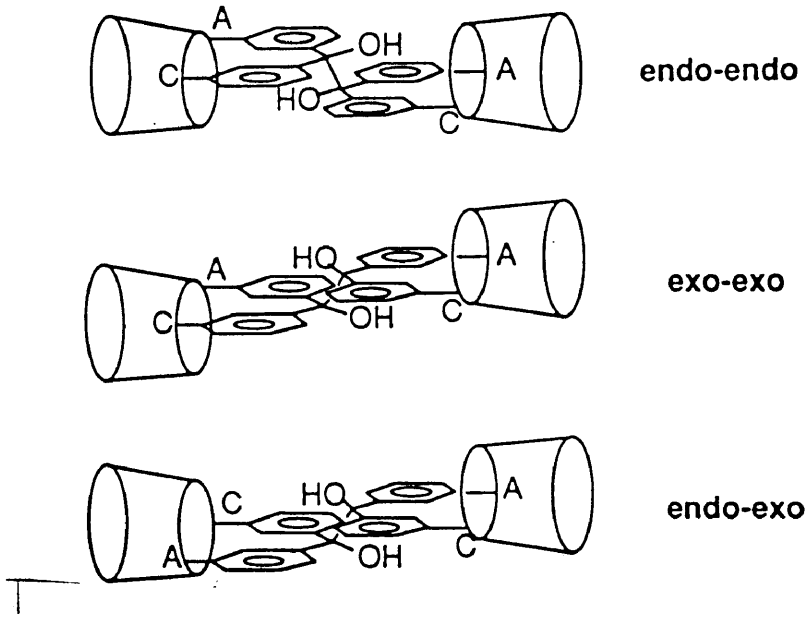
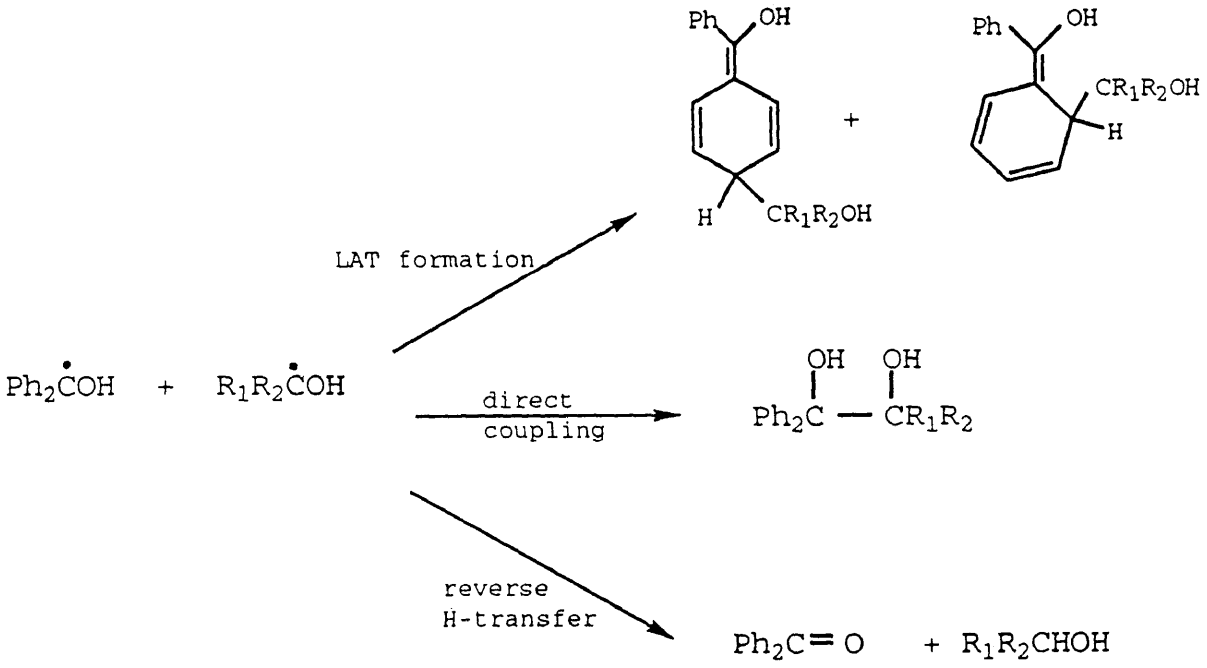


Figure 10. Possible Pinacol Products.

In addition to pinacol formation, other products arise under high intensity irradiation, as can be seen in figure 11. Light absorbing transients (LATS) are created and typically function as quenchers of triplet benzophenone. Direct coupling and reverse hydrogen transfer are also known to occur between benzophenone and the alcohol solution.[11]

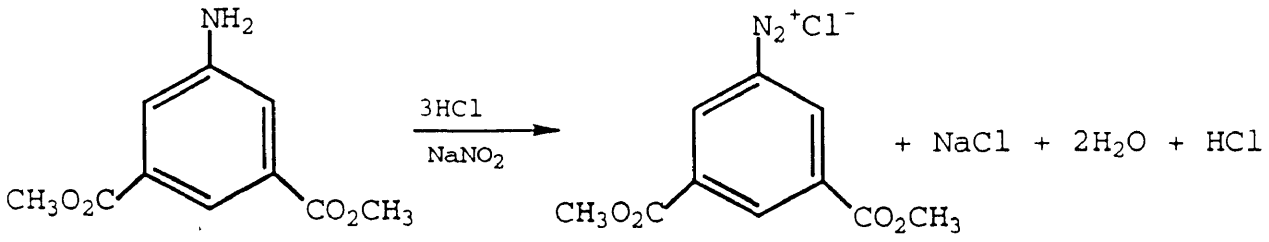
Figure 11. Possible LAT Products.



The photopinacolization of di-tethered β-cyclodextrin has also been investigated. Acetophenone was di-tethered to β-cyclodextrin to form the A-B, A-C, A-D isomers. Because seperation of the three isomers proved difficult, photolysis was not attempted, as it would have resulted in a mixture of four regioisomers and twelve different products. Yet, if seperation of the isomers were possible, joining of the two tethers should occur because of the proximity of the two carboxyl groups. This joining would result in four regioselectively capped cyclodextrins. The molecule which was to be attached to β-cyclodextrin in this project, acetylisophthalic acid has been predicted to undergo a similar radical coupling via photoexcitation to form a pinacol in isopropanol. In studies reported by Weizmann *et. al.*, acetophenone readily forms a pinacol through irradiation with mercury arc. Thus, it can be surmised that, attached to β-cyclodextrin at two sites, the isophthalic acid would undergo the same pinacol formation.[12]

PREVIOUS SYNTHETIC PATHWAYS:

There are several reported synthesis of acetylisophthalic acid, some of which were not successful. The first scheme involved the use of dimethyl 5-aminoisophthalate. The diazonium salt formed by reaction with HCl and $NaNO_2$, was added to acetaldoxime.[13] Copper



Dimethyl 5-animoisophthalate

Figure 12. Production of Diazonium Salt.

sulfate and sodium bisulfite are used to effect the reaction;the former acts as as an electron catalyst whereas the latter reduces the diazonium to an aryl radical. As the arene radical forms, it combines with the acetaldoxime. The amino radical reacts with another aryl radical to produce the oxime and reduced aryl compound. Thus, as the addition occurs; hydrolysis converts the oxime and two esters to the ketone and carboxylic acids. [13]

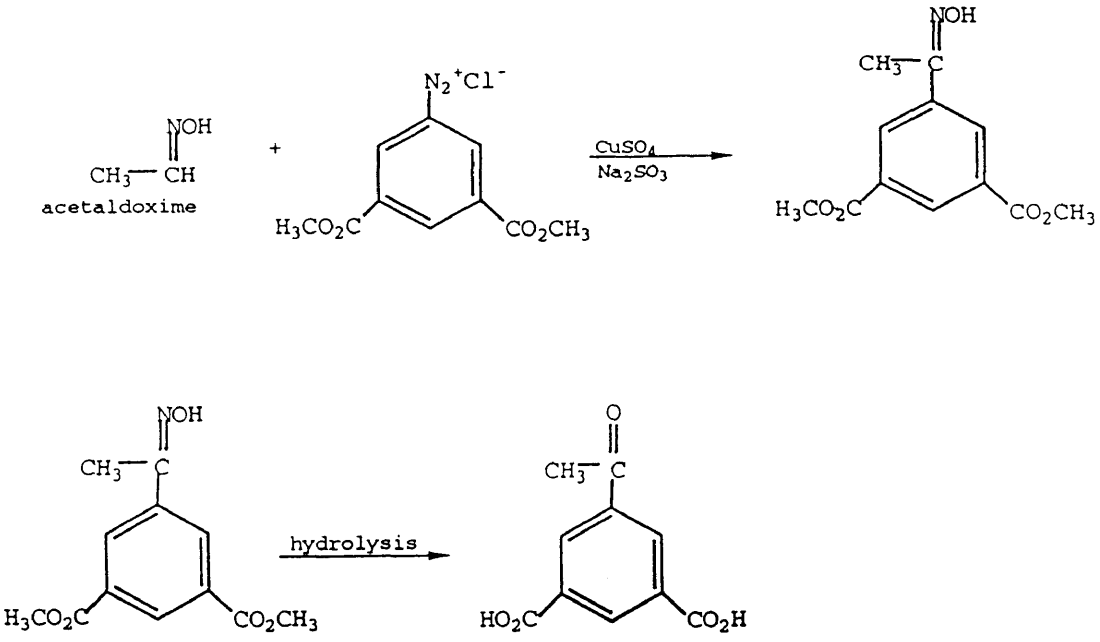
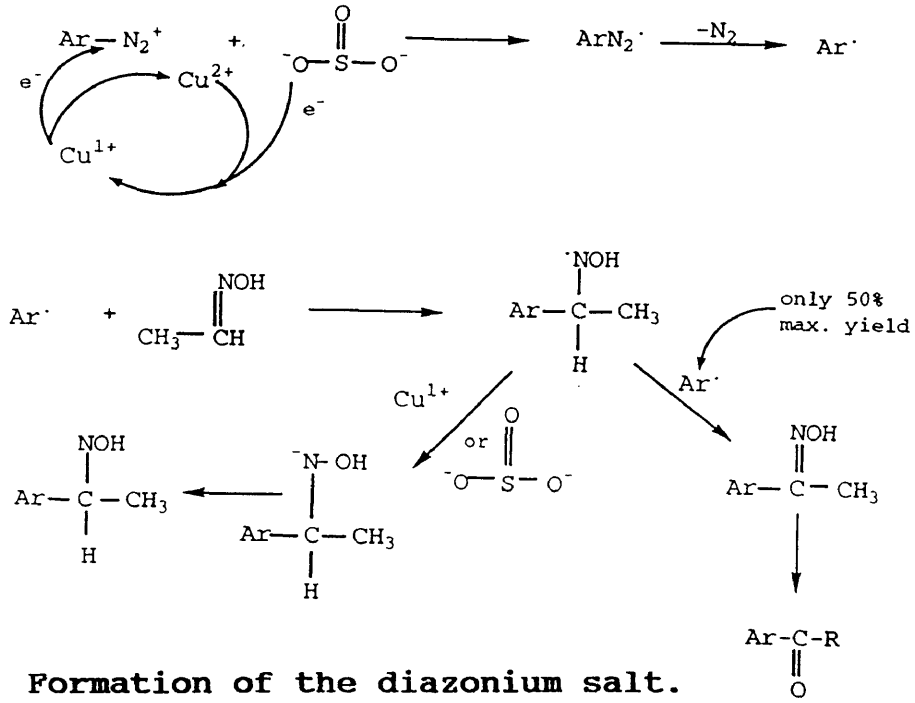


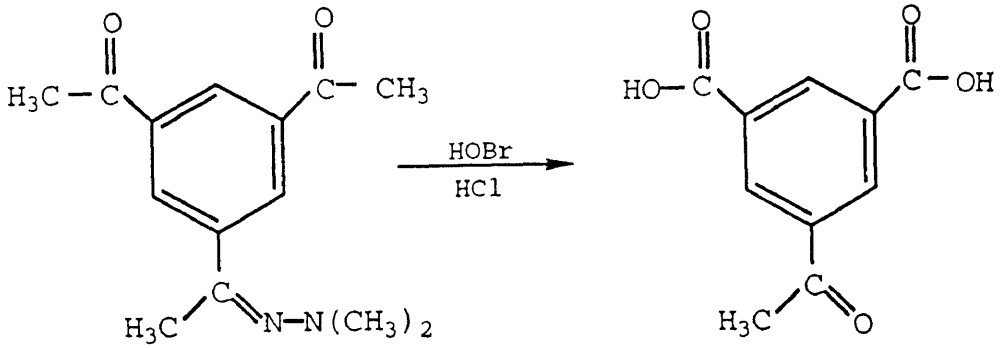
Figure 13. Addition of Acetaldoxime to Diazonium Salt.



Scheme 14. Formation of the diazonium salt.

Although the reported yield was 65%, this procedure was unsuccessful in our hands.

The next synthesis path does not use of the aromatic diazonium salt. Here, the monodimethyl hydrazone of triacetyl benzene is oxidized with HOBr and acidic hydrolysis using HCl to form acetylisophthalic acid.[14]



monodimethylhydrazone of triacetylbenzene

acetylisophthalic acid

Figure 15. Oxidation of Monodimethyl Hydrazone of Triacetylbenzene

The monodimethyl(hydrazone) of 1,3,5-triacetylbenzene was formed by reaction with an equivalent of dimethylhydrazine and triacetylbenzene with p-toluene sulfonic acid in benzene and gave the monosubstituted compound. The dimethyl hydrazone serves as a protecting group and is easily hydrolyzed to the acetyl moiety. Control of the substitution presented a considerable challenge for the successful completion of this synthesis. Often a combination of mono-, di-, and tri-substitution resulted making purification of the compound a troublesome process.

Another suggested pathway involved the reaction of the Grignard reagent made from tribromobenzene with acetaldehyde resulting in 1-(3,5-dibromophenyl)ethylalcohol.[15] The oxidation of the alcohol was troublesome and the route was not pursued further. The results presented here provide a good synthesis of 3'5'-dibromoacetophenone.

Another synthesis attempt involved the bromination of 4-aminoacetophenone using bromine. However, bromine is a strong brominating agent and presented complications by brominating the acetyl group along with the 3'and 5' positions.

OTHER POSSIBLE PATHWAYS:

In addition to the previously investigated pathways, other methods also show promise for the synthesis of acetylisophthalic acid.

One such method currently under investigation begins with the nitration of isophthalic acid at the meta position with fuming nitric acid. Fuming nitric acid is necessary due to the deactivated arene. This reaction is an electrophilic aromatic substitution. The nitro group is subsequently reduced to the amine by catalytic hydrogenation. The amine is then converted to the diazonium salt using HCl and $NaNO_2$. The diazonium salt is reacted with copper cyanide to form a nitrile. Finally, cyanoisophthalic acid is reacted with three equivalents of methyl magnesium bromide and the

product is subjected to acid hydrolysis to convert the imine to the acetyl group.

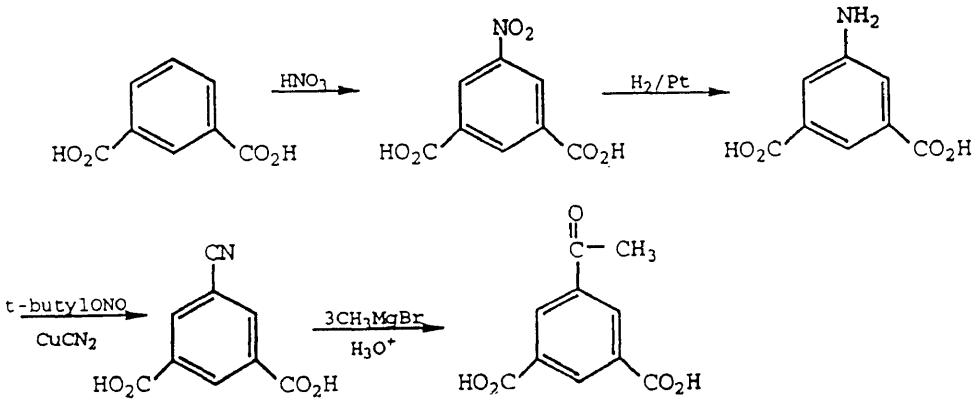


Figure 16. Alkyl Nitrile-Metal Halide Deamination Reaction.

Another possible pathway also uses 3'5'-dibromoacetophenone, the compound used in this research. A protecting ethylene ketal group is formed to block reactions with the carbonyl group. Next the bis-lithiate is generated with t-butyl-lithium. Although this procedure may appear disputable, double metal halogen exchange has been demonstrated. Reaction of the lithiate with two equivalents of carbon dioxide will form the diacid. Finally, the ethylene ketal group is removed by acid hydrolysis. Once the acetyl group is restored, synthesis of acetylisopthalic acid is complete.

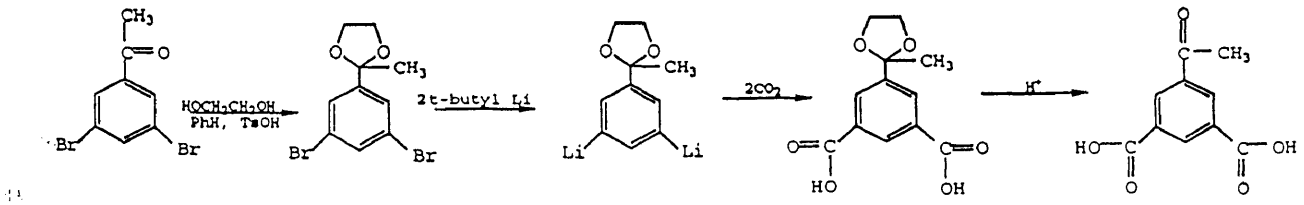


Figure 17. Use of Double Metal Halogen Exchange

The third possible pathway utilizes bromoisophthalic acid. Bromination of electron withdrawing systems has recieved much attention due to the complexity it poses.

In 1950 Derbyshire and Waters brominated benzoic acid with molecular bromine and potassium bromate as a catalyst. It was surmised that the bromate functioned by abstracting bromide ions from the solution which generated hypobromous acids. In acid solution, hypobromous acid is a powerful brominating agent.

$$Br_2 + H_2O \rightleftharpoons H^+ + Br^- + HOBr$$

$$6H^+ + BrO_3^- + 5Br^- \longrightarrow 3Br_2 + 3H_2O$$

Figure 18. Formation of Hypobromous Acids.

Bromination of nitrobenzene was investigated under these conditions and it was found that the bromination was not sensitive to the quantity of molecular bromine or potassium bromide used, but instead, relied upon the amount of potassium bromate used. The reaction was also dependent upon the concentration of sulfuric acid which allowed the decomposition of potassium bromate and generation of hypo
bromous acid in solution. The bromination was also attempted on acetophenone which, when reacted with potassium bromate in sulfuric acid, yielded a 6:1 mixture of *m*- and *o*-bromoacetophenone. Bromination of phthalic acid generated bromopthalic acid in a 50% yield. As a result of these studies, it was concluded that bromination of deactivated

aromatics occurred readily via the described acid bromate system.[16]

Alternative to the bromination of isophthalic acid to would be to begin with 5-bromo-xylene and oxidize the two methyl groups to carboxylic acids. Reaction with two equivalents of sodium hydride and then magnesium will generate the Grignard reagent. The Grignard reagent will react with acetonitrile to form the desired acetyl group.

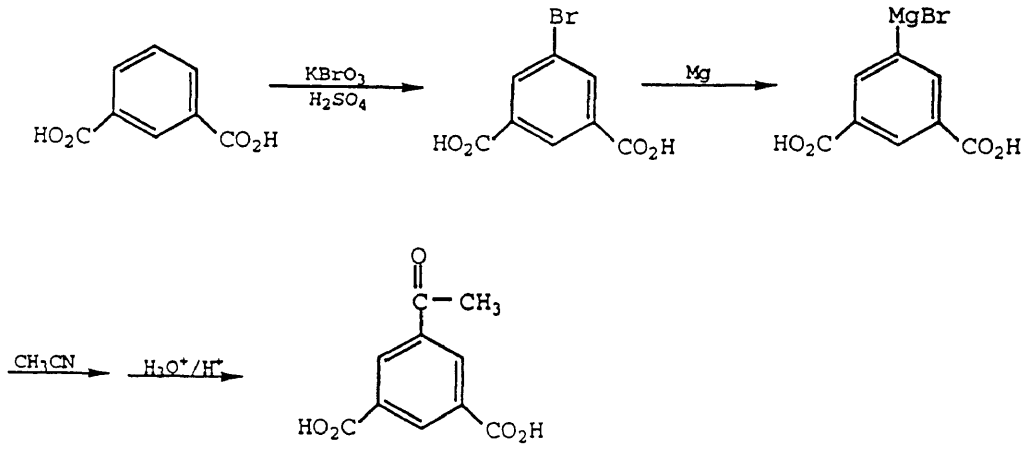


Figure 19. Bromination of Isophthalic Acid and Oxidation to Acetylisophthalic Acid.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were obtained with a GE QE-300 spectrometer. 20-30 mg samples were dissolved in DMSO-d_6 or $CDCl_3$. Melting points were taken on a Mel-Temp capillary m.p. apparatus and are uncorrected. GC-Mass data was obtained on a Hewlett Packard 5890 Series II Gas Chromatograph.

3′,5′ Dibromo-4′-aminoacetophenone:

4′-Aminoacetophenone (5.0 g.,0.37 mol), H_2O (110 mL), and 48% HBr (13 ml) were placed in a 250 ml, 3-neck round bottom flask fitted with a thermometer, condensor and the addition funnel. The reaction was heated with stirring to 70°C whereupon 30 % H_2O_2 (7.7 mL) was added dropwise through an addition funnel and the heat was removed. The exothermic reaction raised the temperature to 85°C. When the reaction cooled to 70°C, it was filtered through a Buchner funnel. The filtrate gave a brown precipitate, which was recrystallized from 95% EtOH giving the dibromide (7.35 g., .025 mol, 67%). mp 180 -184°C. ^{1}H NMR($CDCl_3$) δ 8.01 (s 2H), 2.50 (s 3H)

^{13}C NMR($CDCl_3$) δ 195.1, 146.14, 132.6, 128.9, 107.9, 26.2

3′,5′-Dibromoacetophenone:

Dibromoaminoacetophenone (2.5g, 8.5 mmol) and 95% EtOH (50 mL) were combined in a 250 mL round bottom flask fitted with a thermometer, condenser, and addition funnel. The mixture was heated with stirring until all the solid was dissolved (usually 10-15 min). H_2SO_4 (1.2 mL) was added slowly, dropwise through an addition funnel followed by a solution of $NaNO_2$ (1.6 g,.032mmol) in H_2O (20 mL) and a catalytic amount of Cu powder (.30g). The reaction was heated for 2 hrs after which this procedure was repeated. The solution was then filtered by gravity and the solid was recrystallized from 95% EtOH and H_2O.

The solid was purified by sublimation (104°C, 0.1 Torr) giving the pure deaminated compound in the form of a white solid (1.36g, .48 mmol,54 %) ^1H NMR($CDCl_3$)

δ 8.03 (s 2H), 7.88 (s 1H), 2.58 (s 3H)

^{13}C NMR ($CDCl_3$) δ 139.5, 137.3, 131.3, 123.7, 27.7

3′,5′-Dicyanoacetophenone:

3,5 Dibromoacetophenone (1.0g, .36mmol) was combined with CuCN (1.30g, 1.45 mmol), $CuSO_4$ (.1 g, .062mmol), and 5 mL deionized H_2O in a sealed tube and heated for 24 hrs at 210°C in an oil bath and allowed to cool. KCN (1.0 g,1.53 mmol) was added to the tube and it was reheated for 24 hrs at 240°C. After cooling the tube, the contents were heated to boiling in the opened tube. The contents were then filtered by gravity and the filtrate was acidified with H_2SO_4 (15 mL, 15.2 mmol) giving a white precipitate. The contents of the flask were diluted with 1000 mL deionized H_2O and filtered with a Buchner funnel. A white solid resulted (.63g, 0.36 mmol, 63%). ^1H NMR ($CDCl_3$) δ 2.51 (s 3H), 8.05 (s 2H), 8.13 (s 1H)

3′,5′-Dibromoacetophenone ethylene ketal:

3′,5′-Dibromoacetophenone (1.0 g, 0.36 mmol) was combined with ethylene glycol (5.0g, 8.06 mmol), benzene (50mL), and a catalytic amount of *p*-toluene-sulfonic acid in a 250 mL round bottom flask fitted with a Dean-Stark trap, condenser and heating mantle. The solution was heated to reflux with constant stirring. Benzene was removed by distillation and 50 mL H_2O was added. The mixture was extracted with ether (3X100 mL). The ether layers were concentrated *in vacuo* and purified by sublimation (104°C, 0.1 Torr) giving the ethylene ketal. (0.43g, 0.132 mmol, 43%) ^1H NMR($CDCl_3$) δ 8.00 (s 2H), 7.8 (s 1H), 4.10 (s 2H), 3.8 (s 2H), 2.6 (s 3H)

1-(3,5-Dibromophenyl)ethanol:

3′,5′-Dibromoacetophenone (1.5g, 0.54 mmol) was dissolved in 40 mL methanol (125 mmol) with constant stirring. A solution of $NaBH_4$ (0.5g, 1.3 mmol) in 20 mL deionized H_2O was added dropwise to the solution. A dilute solution of H_2SO_4 was added (3-4 drops) until the solution reached a neutral pH. The methanol was removed by concentration *in vacuo*. The solution was extracted with ether (3x100 mL) and concentrated *in vacuo*. The oily substance was purified by sublimation (104°C., 0.1 Torr) giving the pure alcohol compound as a white solid (1.04g, 0.37 mmol, 69%).

^1H NMR ($CDCl_3$) δ 7.56 (s 1H), 7.44(s 1H), 4.83 (q 1H), 1.47 (d 3H)

^{13} NMR ($CDCl_3$) δ 149.9, 133.2, 127.5, 123.2, 69.4, 25.5

1-(3,5-Dicyanophenyl)ethanol:

A 0.5 g sample (0.18 mmol) of 1-(3,5-dicyanophenyl)ethanol was mixed with 2.0 g. (2.23 mmol) CuCN in distilled dimethylacetamide (DMAC) (10 mL) in a 100 mL round bottom flask and heated to reflux for 6 hrs. The mixture was then diluted with 50 mL of deionized H_2O. The hot mixture was added to a solution of 1:1 ammonium hydroxide/H_2O (80 mL) and methylene chloride (250 mL). The solution was allowed to stir overnight. The mixture was transferred to a separatory funnel and the aqueous layer was removed. The remaining methylene chloride layer was washed with deionized H_2O (5x100 mL) to remove residual DMAC, dried over $MgSO_4$, and concentrated *in vacuo*. The oily substance was purified by sublimation (104°C,0.1 Torr) resulting in a solid, . 0274g (.0001 mmol, 5.4%)

^1H NMR ($CDCl_3$) δ 7.86 (s 2H), 7.775(s 1H), 4.90 (q 1H), 1.50(d 3H)

^{13}C NMR ($CDCl_3$) δ 149.6, 133.4, 133.2, 116.9, 113.9, 68.4, 25.5

RESULTS AND DISCUSSION

The primary goal of this research project was to synthesize acetylisophthalic acid as a double capping agent for cyclodextrin. Although the capping of cyclodextrin with this molecule was the eventual goal, challenges present in the synthesis of the acid made it the focus of this project. As mentioned earlier, several pathways were attempted, but were not successful. The final pathway pursued is outlined below and consisted of a process starting with 4'-aminoacetophenone.

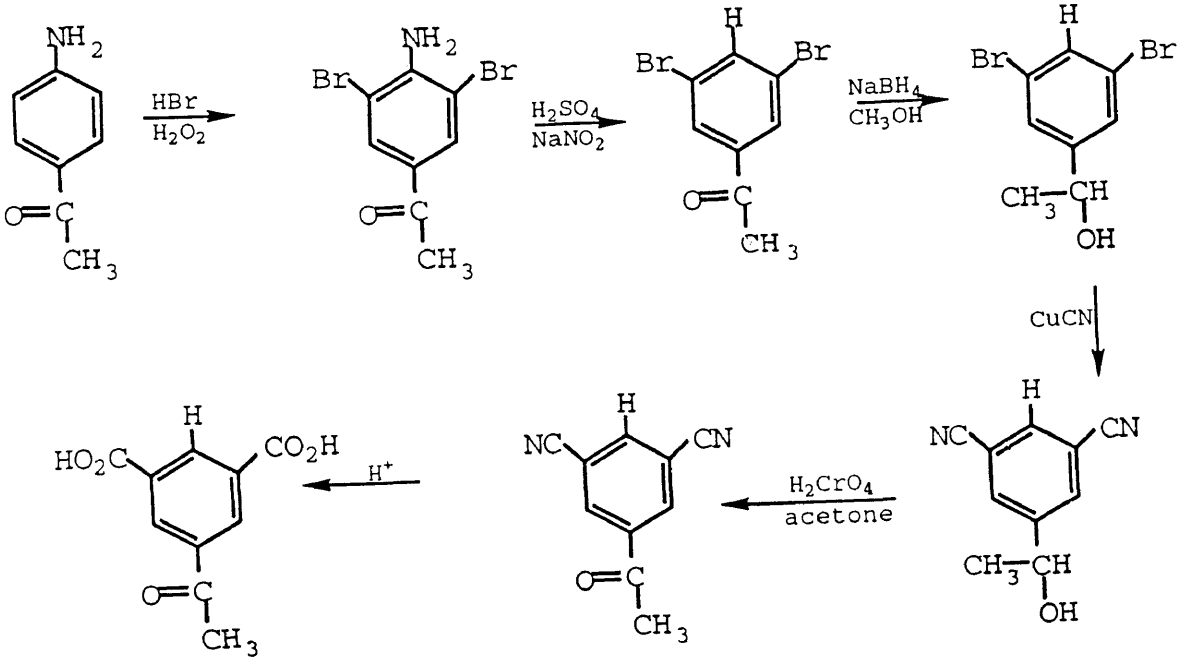


Figure 20. Complete Pathway.

Ultimately, the corresponding diacid chloride would have been used to double cap β-cyclodextrin. Subsequent irradiation would presumably lead to pinacol formation.

The first step in this pathway involves the bromination of 4′-aminoacetophenone. In order to brominate at both the 3′ and 5′ position, HOBr was used as opposed to

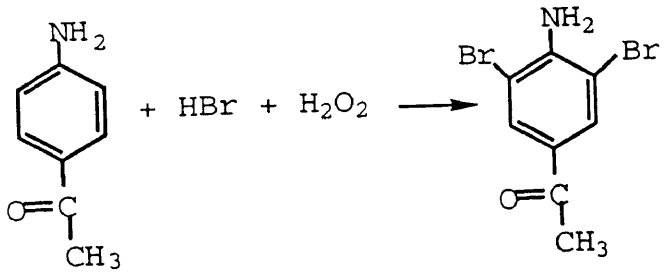


Figure 21. Bromination of 4′-Aminoacetophenone.

Br_2. The use of HOBr allowed the regiochemistry of the reaction to be better controlled by preventing bromination of the acetyl group. HOBr is generated in situ by the addition of 30% H_2O_2 to a solution of 48% HBr. The mechanism is an electrophilic aromatic substitution, which proceeds via a positive arenium ion. A base (Br^- or H_20) then abstracts the aryl proton, restoring the aromaticity and leaving the ring brominated.

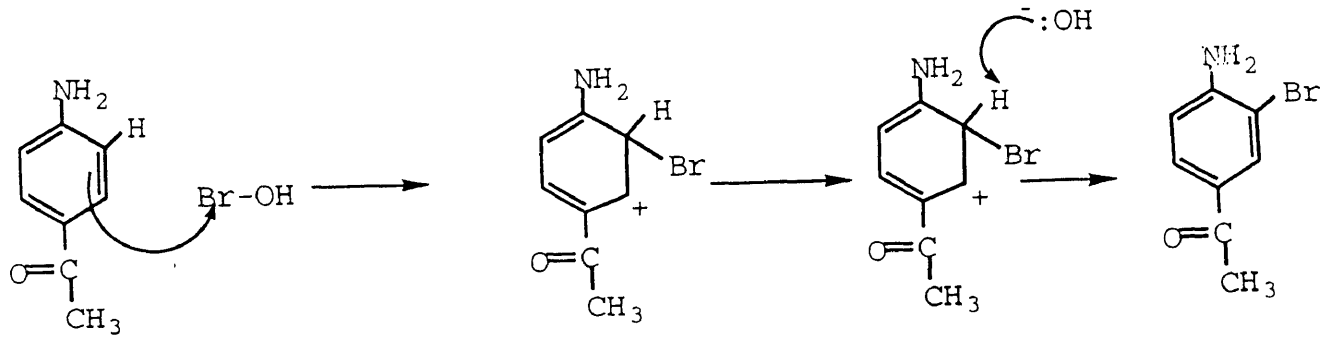


Figure 22. Mechanism for bromination of 4'Aminoacetophenone. Bromination does not occur on the methyl group of the acetyl because bromination can only occur when this acetyl is present in the enol form. The hypobromous acid reacts as $Br\text{-}^{+}OH_2$, which is more reactive than Br_2. Thus the electrophilic aromatic substitution can proceed at a faster rate than reaction with the low concentration of enol. Br_2 will more readily brominate the acetyl group.

The amino group which donates electron density to the ring and accelerates the bromination is removed in the next step. This reaction proceeds by decomposition of a diazonium salt.

Water soluble diazonium salts are produced by reaction of primary amines and nitrous acid. The diazotization occurs by addition of concentrated sulfuric acid followed by the addition of sodium nitrate which combine in solution to form nitrous acid. One can test for the presence of excess nitrous acid by using a starch iodide paper.[17]

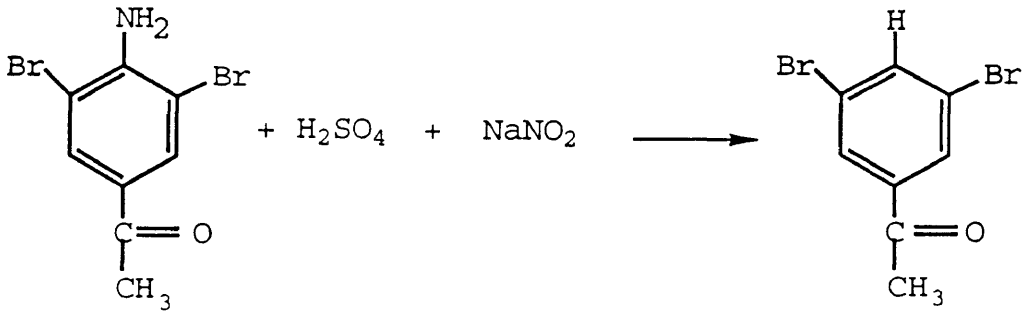


Figure 23. Deamination of 3′,5′-Dibromoaminoacetophenone.

Once the diazonium group is present, it can be replaced by a number of different groups, including hydrogen, halogens, psuedohalogens, aromatics, metals, sulfur, and arsenic containing groups through a nucleophilic substitution or a free radical reaction . The present synthesis required replacement with a hydrogen. This reaction proceeds via aryl radicals which are formed through the decomposition of aryldiazenyl radicals. [18]

The third portion of this synthesis involved the cyanation and subsequent hydrolysis to the desired carboxylic acid in the same reaction vessel. This method was reported in the literature in 1932, and first performed using an Autoclave heated to 200°C. The solid was collected and purified via a Soxhlet extraction.[19] Here a slightly modified version was attempted using a sealed tube heated to approximately 220-240°C. This reaction, a slightly altered form of the the Rosenmund von Braun reaction, was performed using a KCN, CuCN, H_2O, and a catalytic amount of $CuSO_4$. The dibromoacetophenone undergoes a double nucleophilic aromatic substitution. The KCN serves to decompose the copper complex and accelerate the hydrolysis to the diacid.

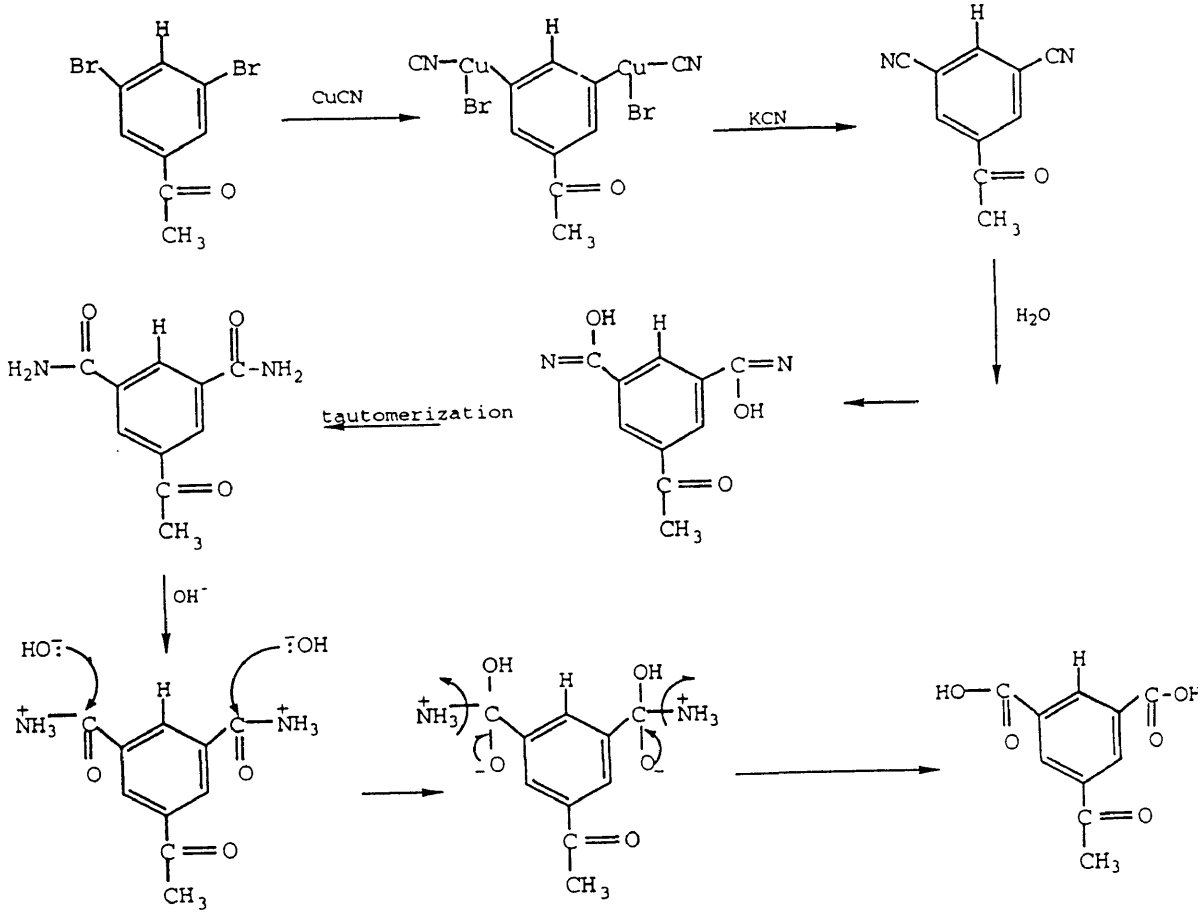


Figure 24. Mechanism for Cyanation and Hydrolysis.

By heating the reaction under increased pressure, it was assumed the reaction would undergo complete conversion. Because successful results were not achieved, the reaction

conditions were varied. A variety of solvent systems, reaction times, and reagant amounts were tested.

SEALED TUBE CYANATIONS

#	YIELD	CHARACTERIZATION (REACTION CONDITIONS)
1	0.21g	11 hrs @ 220°C/ recrystallization in H_2O/EtOH
2	-	22 hrs @ 163°C/recrystallized in H_2O/EtOH
3	0 .06g	11 hrs @ 220°C/Recrystallized in benzene-acetone
4	-	7 hrs @ 180-200°C
5	0 .11g	6 hrs @ 180-200°
6	1.65g	12 hrs @ 220°C,no KCN used,1.5g CuCN, Nitric Acid digestion
7	0.43g	20 hrs @ 220°C,no KCN, 1.30g CuCN nitric acid digestion
8	-	20 hrs @ 220°C,1.3g,solvent-1:4 H_2O:pyridine
9	-	8 hrs @ 220°C, solvent 1:2 H_2O:pyridine
10	0.40g	18 hrs @ 220°C, 1.3g, CuCN
11	1.05g	20 hrs @ 220°C, 0.65g CuCN,0.5g KCN,stir bar
12	1.67g	20 hrs @ 220°C, 1.3g CuCN,.5g KCN, .1g $CuSO_4$,stir bar
13	0.03g	24 hrs @ 220°C, 0.10g $CuSO_4$, stir bar
14	0.26g	20 hrs @ 220°C, used $NH_3OH/H_2O/H_2SO_4$ work up method
15	0.39g	20 hrs @ 220°C, same conditions, solvent 50/50 H_2O/DMSO
16	0.63g	work up- hot filtration, acidify, 240°C, then same as number 14

The strongest indication that all these procedures failed came from the continually poor results of recrystallization attempts. The literature stated that the solid would recrystallize in a mixture of benzene and acetone. Differing concentrations were used but the solid was not soluble in any mixture of the two. Other solvent systems were used such as 1,2 dichloroethane, 1,2 dichloroethane/acetonitrile, ethanol/H_2O, benzene, benzene/acetone and toluene, acetic acid /toluene, toluene/dimethylsulfoxide (DMSO), and acetonitrile/toluene.

A derivatization with thionyl chloride was also done, followed by attempts at recrystallization, but poor yields and impurities resulted. Because the results attained by this method were far from satisfactory, the normal Rosemund von Braun procedure was attempted. The only modification here was changing the solvent to dimethyl acetamide (DMAC), an aprotic and high boiling solvent which prevent subsequent hydrolysis.

The Rosenmund von Braun reaction is a nucleophilic aromatic substitution. Usually, such a reaction requires a relatively strong leaving group and activation of the

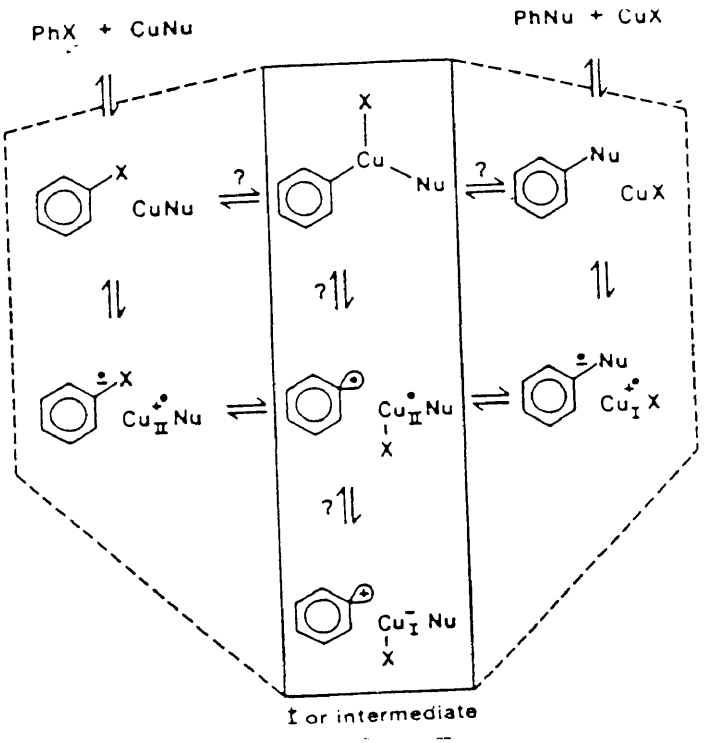


Figure 25. Possible Mechanisms for Rosenmund von Braun Reaction.

aromatic ring by electron withdrawing substituents to stabilize the negative charge brought about by the addition-elimination mechanism. Yet, it has been found that copper mediated reactions are effective for nucleophilic aromatic substitutions on unactivated aromatic rings. Although evidence exists for such copper mediated substitutions, a thorough mechanistic explanation has not been derived. Suggested pathways include a benzyne mechanism, non-chain electron transfer or radical mechanisms, the $S_{RN}1$ radical chain mechanism, and a concerted mechanism. Because of a lack of substantial evidence for the other pathways, the concerted mechanism is the most widely accepted mechanism.

The benzyne mechanism has lost credibility because it does not result in expected retention of substitution on the ring.The $S_{RN}1$ radical chain mechanism, and all non chain electron transfer mechanisms are discounted due to lack of inhibition by radical or electron traps.

The concerted mechanism is most widely because of the lack of a better alternative. It operates via an intimate electron transfer form the copper-nucleophile to the aromatic halide forming a radical ion pair trapped in a solvent cage. The radicalion pair readily converts to the ligand exchange product.[20]

The original starting material, 3'5' dibromoacetophenone, presented a number of obstacles to cyanation. The acetyl group caused the most difficulty since it is electron withdrawing and deactivated the ring. Another potential problem was the basicity of CN^- ion itself. The cyanide may be able to enolize the acetyl group resulting in aldol like reactions , including trimerization.

One attempt to rectify this situation involved the use of a lithium aluminum hydride reduction to reduce both the cyano and carbonyl groups. $LiAlH_4$ is a commonly used reducing agent for various acids, aldehydes and ketones and is much stonger than sodium borohydride. Unfortunately, this reduction was performed on the solid collected from the sealed tube cyanation, which was assumed to be

acetylisophthalic acid. The most critical phase in this reduction is the transfer of a hydride ion from the metal to the carbonyl carbon. The hydride ion acts as a nucleophile, leaving the aluminum compound as a Lewis acid that acts as an electrophile at the carbonyl oxygen, allowing the hydride transfer.[21] The reduction did not succeed, yet it would be expected that the acetyl group would undergo conversion to its analogous alcohol. This did not occur either.

In an effort to counteract the electron withdrawing effect of the acetyl substituent and prevent trimerization, the acetyl group was turned into a ketal. By using a solution of diethylene gylcol, dissolved in benzene, with a catalytic amount of *p*-toluene sulfonic acid, formation of the cyclic ketal proceeded successfully. The mechanism behind this reaction starts by a protonation of the acetyl group
and proceeds through a series of nucleophilic substitutions. Once the carbonyl group was protected, the cyanation reaction was tried once more. Analysis of ^{1}H NMR of the molecule before and after a cyanation attempt revealed that the the protecting group did not remain on the molecule long enough to allow cyanation to occur in the absence of the acetyl group.

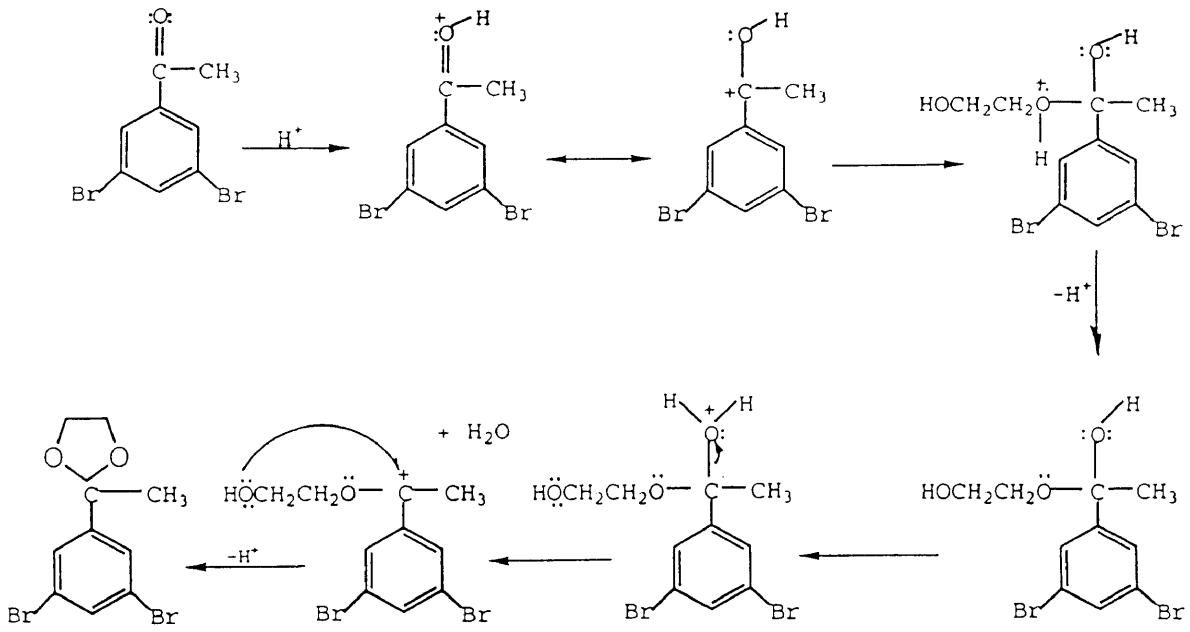


Figure 27. Addition of Ethylene Ketal Protecting Group.

Attempts at modifying the acetyl group to make it less base sensitive were abandoned for an alternate reaction pathway: the Rosenmund von Braun reaction. This reaction was first performed using the original starting material 3′,5′ dibromoacetophenone .

It was expected that the product would easily extract into the ether layer just as the original dibromoacetophenone, yet the extraction of the product into the organic layer did not happen easily. A continuous extraction using a solution of 10% ammonium bicarbonate, H_2O, and ether was run for about six days. An examination of the GC/MS Spectrometer data established the presence of a 3′- cyano-5′ bromoacetophenone. Based upon, this information, the Rosenmund von Braun reaction was performed

for a more extended period of time, yet the same results were not obtained. Different methods of working up the reaction were also investigated such as an ammonium hydroxide/H_2O decomplexation and a nitric acid digestion.

Because the Rosenmund von Braun reaction with 3',5' dibromoacetophenone was not satisfactory, another modification to the acetyl group was tried. A sodium borohydride reduction was performed to convert the acetyl group to a secondary alcohol making the moiety less base sensitive. It was surmised that using $NaBH_4$ would be more successful in reducing the acetyl group due its milder nature.

Once the alcohol was formed, cyanation was attempted again using the same Rosenmund von Braun procedure in DMAC. ^1H NMR data showed the (dicyanophenyl)ethanol had formed but in a very minute yield.

Ideally, the dicyanophenylethanol should be oxidized back to the acetophenone and subsequently acidified to the diacid. Because the dicyanophenylethanol was not attained in high enough yield, these methods were not attempted.

If the diacid were synthesized it would be employed in the double capping of β-cyclodextrin with the acetylisophthalic acid. This would be carried out by a chlorination of the acid groups through a reaction with

thionyl chloride, DMF, and acetylisophthalic acid. Once the capping agent is obtained, it would be added to a solution of β-cyclodextrin and pyridine at 60°C . This method, previously developed by Tabushi [8], requires that the pyridine be fractionally distilled and stored over molecular sieves. Cyclodextrin must be dried overnight *in vacuo* at 100°C prior to the reaction . Once the reaction is performed, the solution of cyclodextrin in pyridine must be distilled once again to remove traces of complexed water left after the drying of cyclodextrin. Following this distillation, the capping agent is added to the pyridine distilled *in vacuo* and heated at 60°C for 3 hours. The product is dried overnight *in vacuo*.

Double capping of the cyclodextrin should happen at the A,B glucopyranose units, and due to spacing, at the E,F or D,E units. If the double capping occurs successfully, photolysis would allow for pinacolization. The pinacol forms by the introduction of UV light into a solution of the capped cyclodextrin solvated in isopropanol. The UV light results in an n-Π^* transition of the carbonyl, leaving the oxygen with an unpaired electron which abstracts a hydrogen atom from the isopropanol. The resulting carbonyl carbon radical couples with another to form a pinacol.

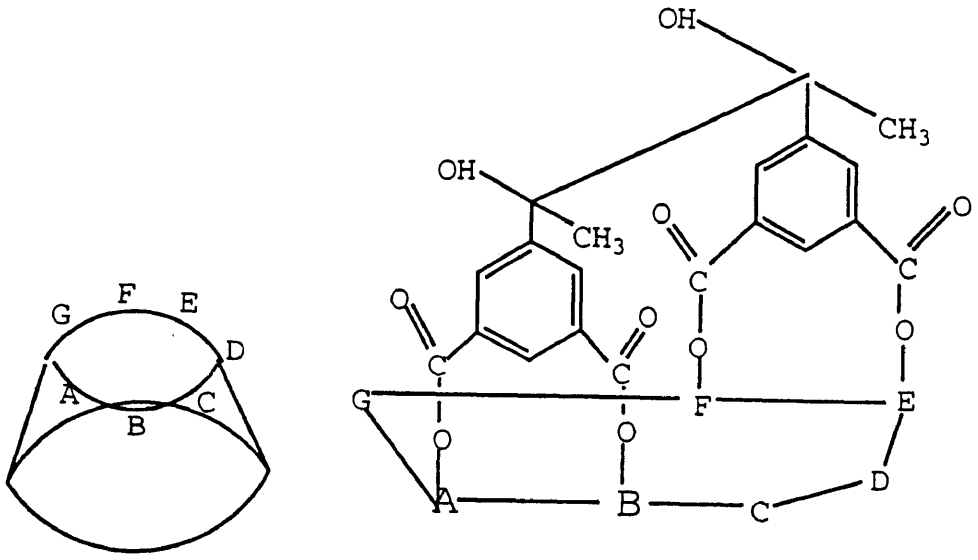


Figure 27. Double capping and Pinacolization of Acetylisophthalic Acid to β-cyclodextrin.

CONCLUSION

Although several methods of synthesizing Acetylisophthalic acid were attempted, none were completely successful. Results from ^{1}H NMR proved that 1-(3′,5′-Dicyanophenyl)ethanol was synthesized, but in poor yield. 1-(3′,5′-Dicyanophenyl)ethanol requires further oxidation to 3′,5′-Dicyanoacetophenone which can then be hydrolyzed to acetylisophthalic acid.

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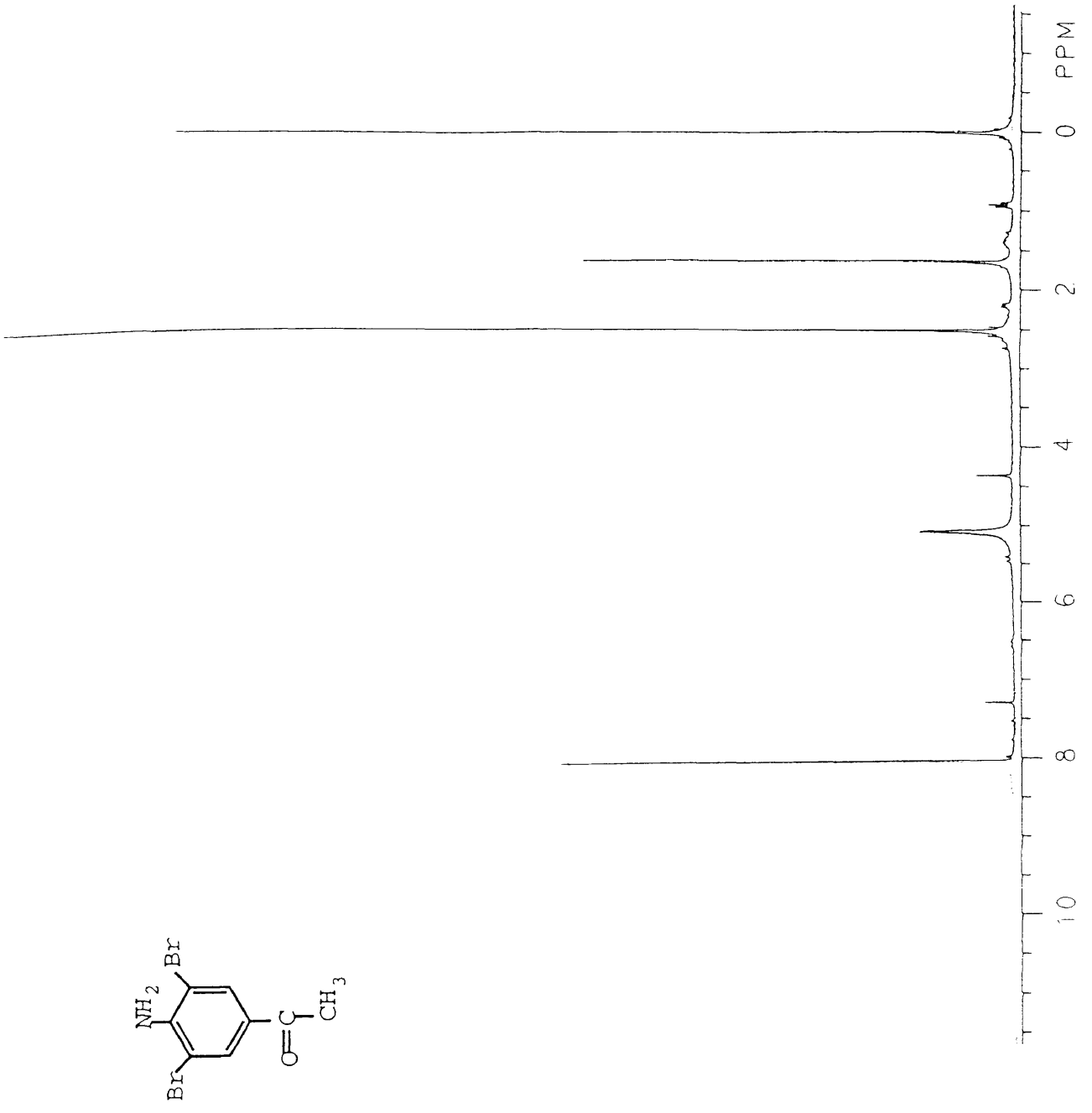
APPENDIX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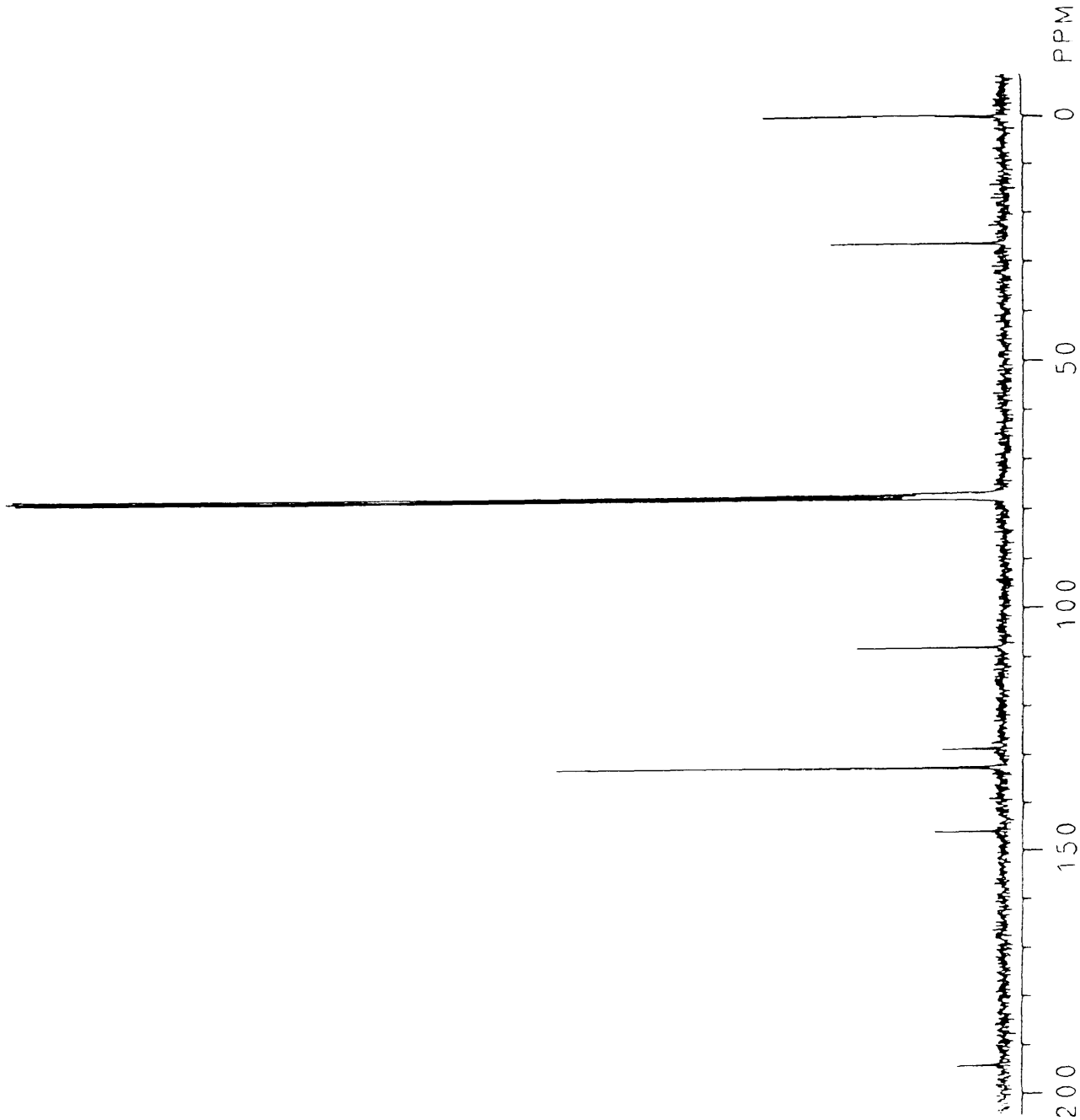
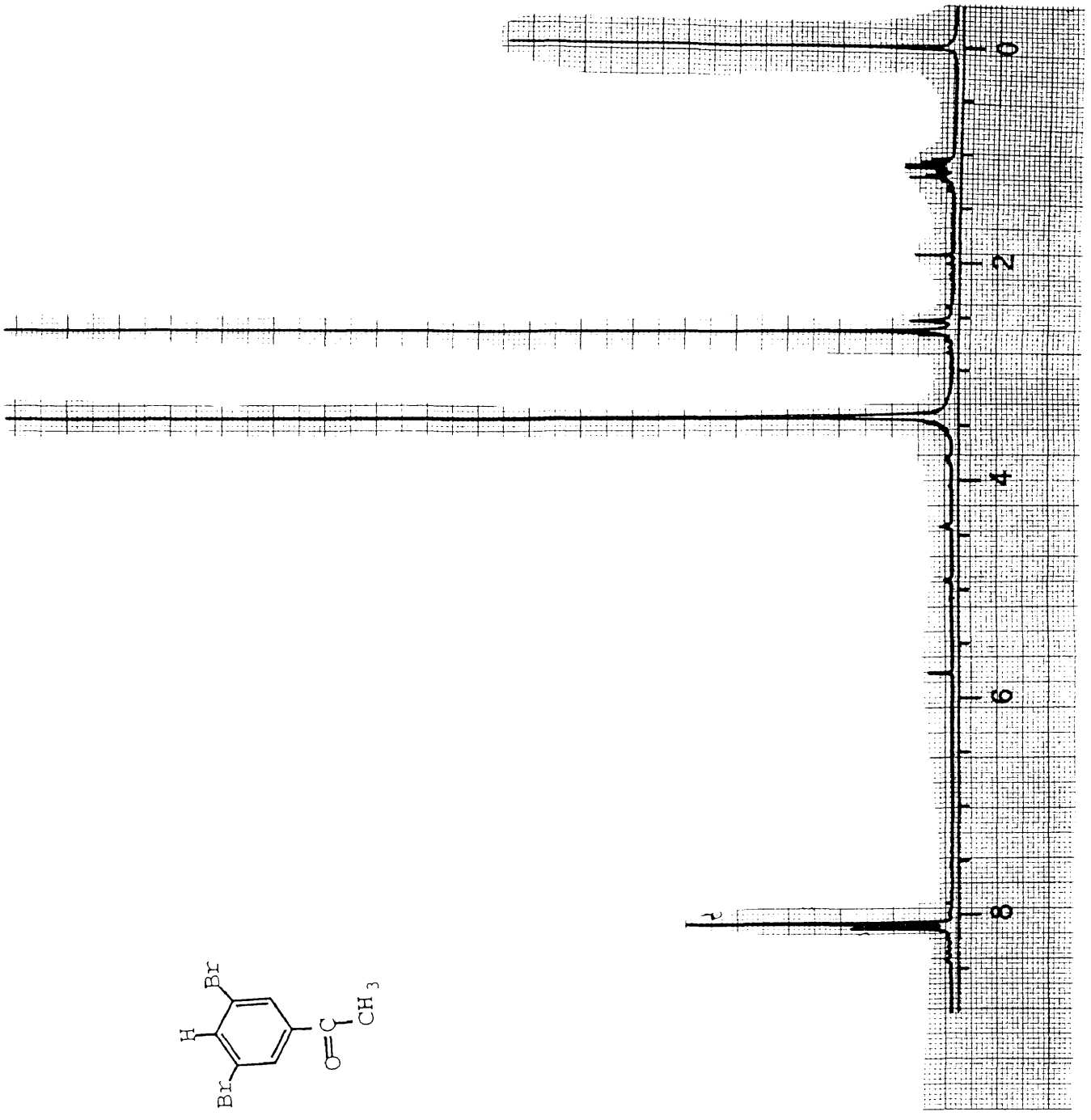
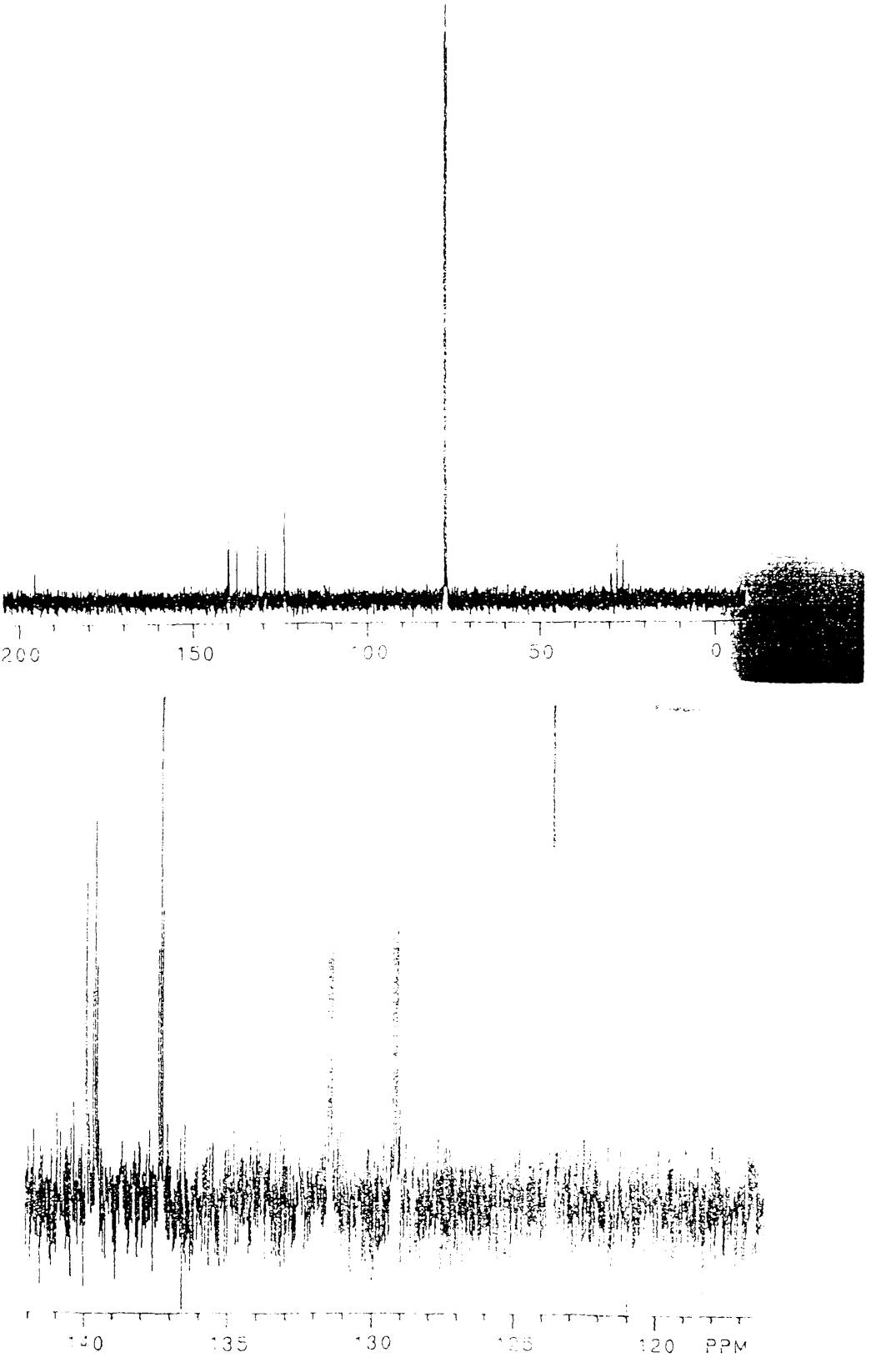
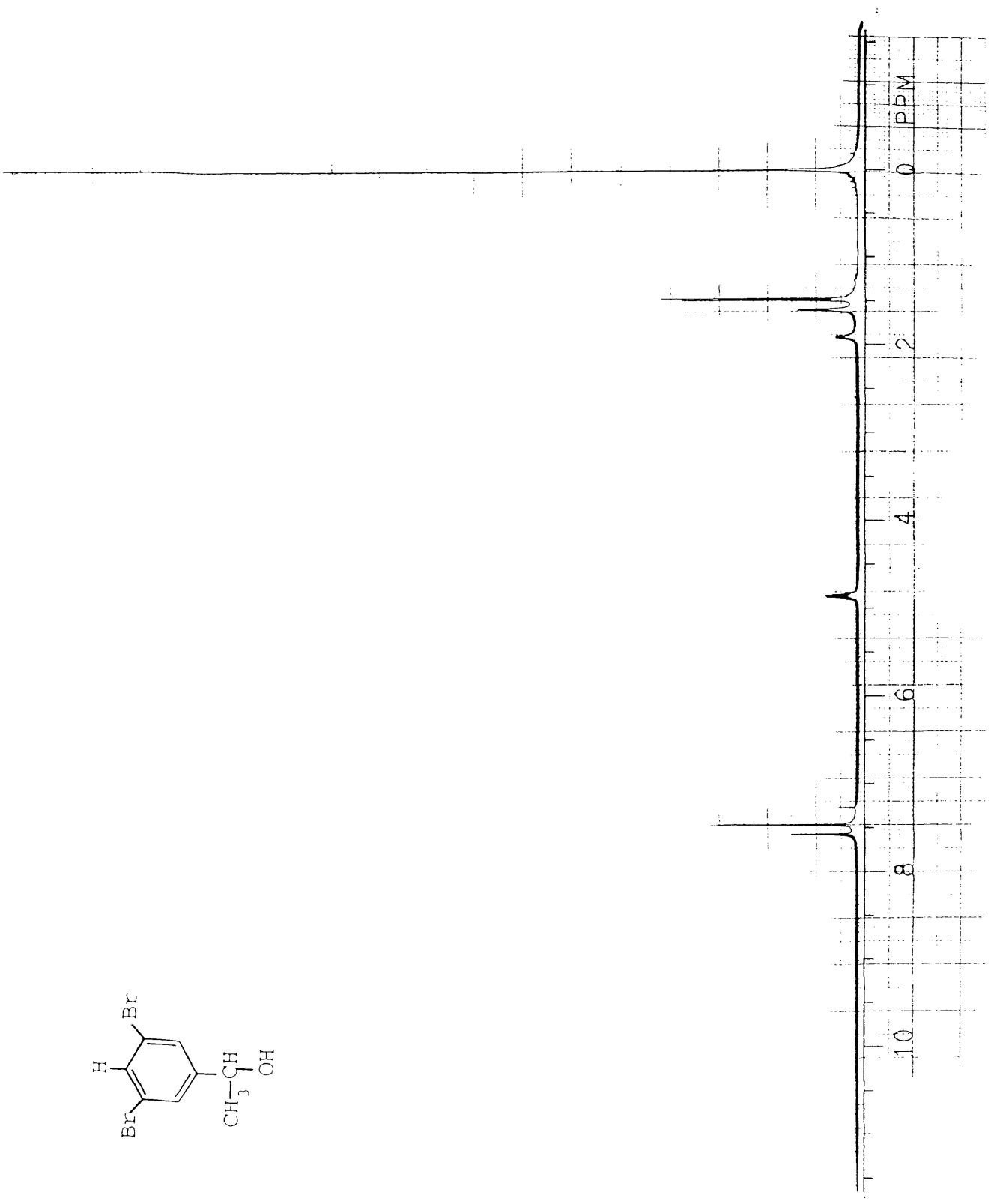
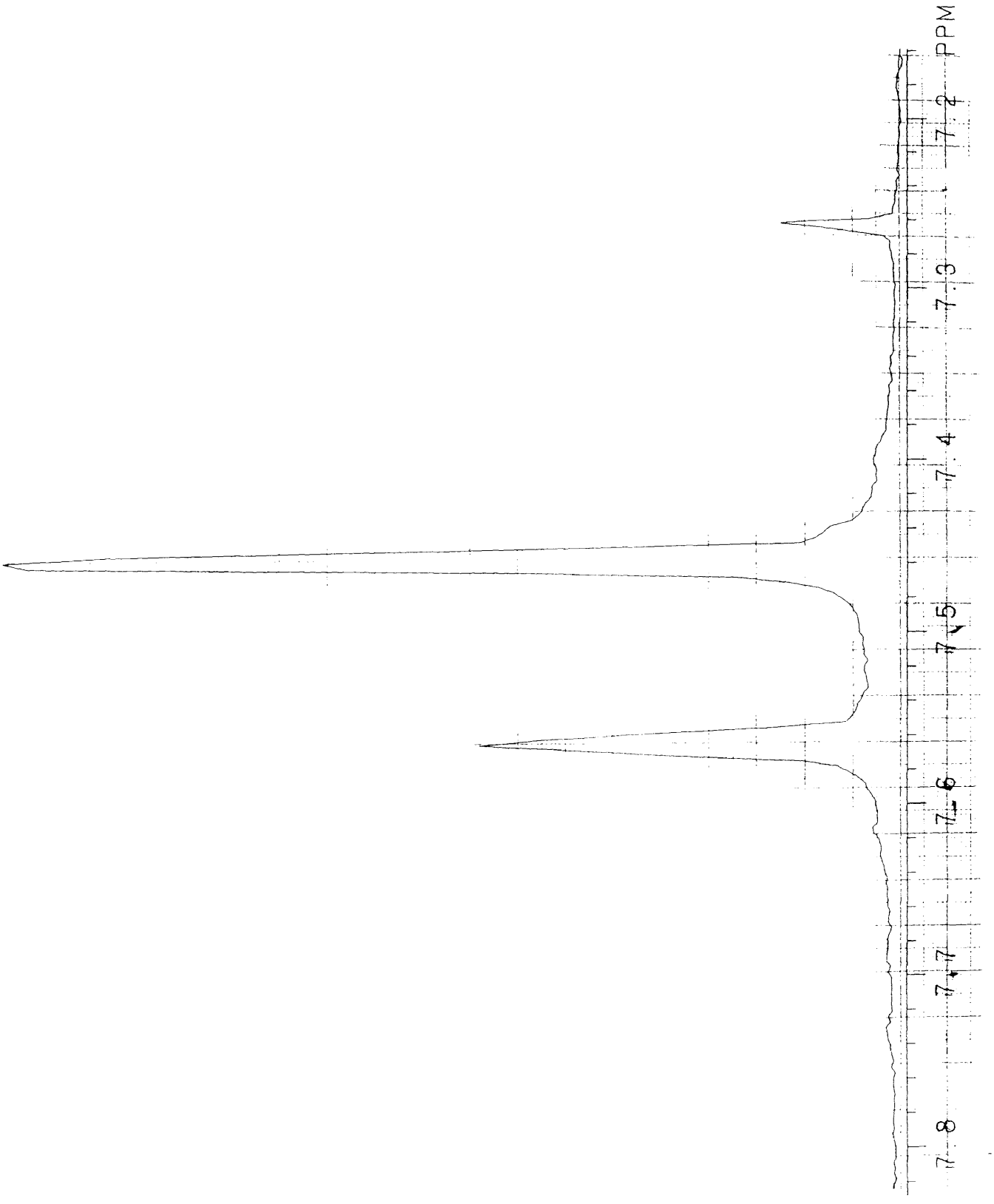
O
CH3


PPM
0
50
100
150
200

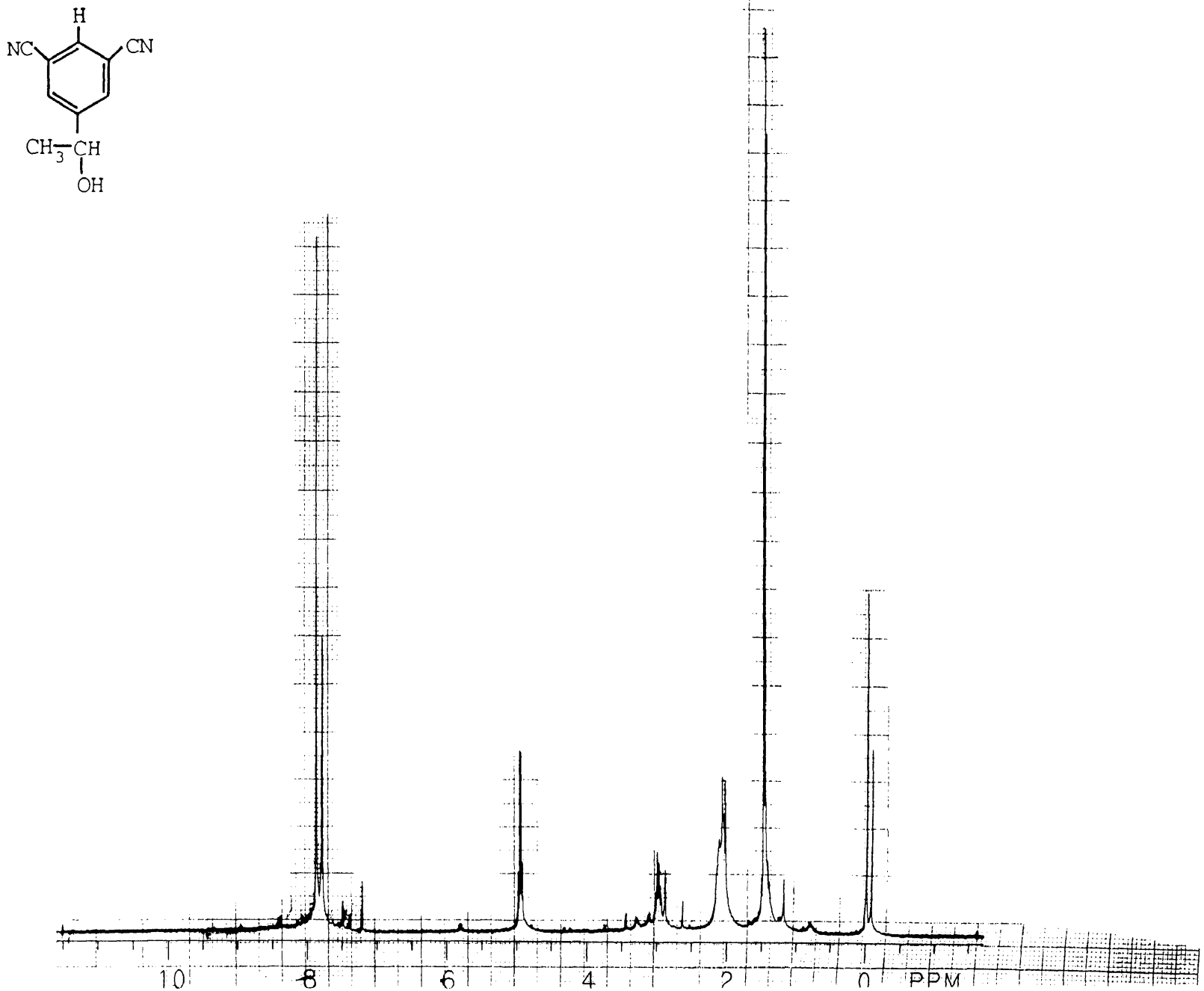

0
2
4
6
8
Br
H
Br
O
CH3


200
150
100
50
0
140
135
130
125
120
PPM


Br
H
Br
CH3
CH
OH
PPM
0
2
4
6
8
10

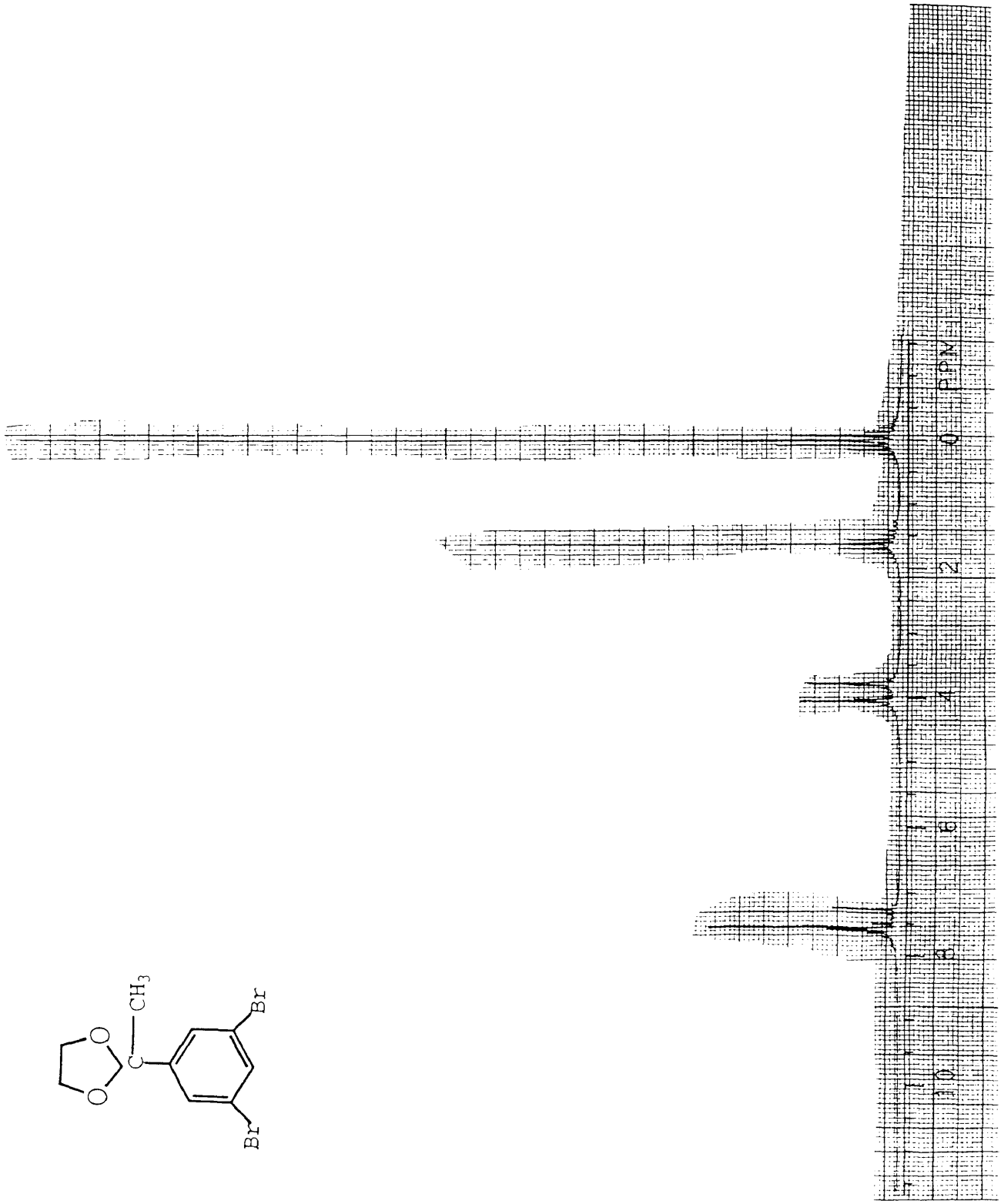

PPM
7.2
7.3
7.4
7.5
7.6
7.7
7.8

PPM
20
40
60
80
100
120
140


H
NC
CN
CH3 CH
OH
10
8
6
4
2
0
PPM

7.65 PPM
7.70
7.75
7.80
7.85
7.90

ppm
0
50
100
150
200


8.0 ppm
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
CH3
C
O
O
Br
Br

VITA

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